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Containing a Symposium on Traumatic "Shock"

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BRITISH JOURNAL OF ANAESTHESIA

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EDITORIAL

THE ANAESTHETIST AND "SHOCK"

LEAN old men with stout hearts, with hearts damaged by previous infarction; fat young women with mitral stenosis; patients with dehydration; peritonitis; intestinal perforation; or obstruction; diabetes; anaemia; carcinoma; chronic bronchitis and emphysema; all these and many more besides, are compounded singly or in multiples, into the sum of clinical practice where art competes with science and experience teaches by much trial and error.

Art can be learnt almost entirely by instinct from practice but science is a harder path leading, it is to be hoped, onwards where instinct can only follow; however, sometimes instinct, in the form of a clinical impression, leads the scientist.

One clinical impression which is almost universally held is that major surgical procedures with minimal bleeding under light anaesthesia do little harm unless vital structures are involved.

The great controversies of "shock" continue to rage even amongst the scientists of today, leaving the anaesthetist to act upon his own initiative when faced with the problems set by patients with disorders of the circulation after injury. The aim of this symposium is to give anaesthetists some idea of the extent and content of recent work on "traumatic shock" so that it can be orientated with clinical practice. Some may be dismayed to learn that the simple methods for measuring blood pressure with a cuff and a mercury manometer are not as accurate as they had assumed.

What happens to the heart with a severe fall in systolic blood pressure, as measured by cuff and manometer under the conditions set by anaesthetics in the normal or abnormal patient, would take a long time to tell, even if such knowledge was forthcoming, as it is not at the present time. Some of the results of cardiac ischaemia are revealed in this symposium.

Anaesthetists, possessing a large number of agents and a variety of different techniques at their disposal, can, if they understand something of the disordered state of their patients, plan more rationally their own procedures so as to function as an active partner in the surgical team.

Much depends upon resuscitation in the handling of injured patients, and if the illness is mainly due to loss of blood, recovery will depend on how soon the circulation can be restored; if infection is the offending cause, the patient's life depends upon antibiotic therapy. Infection can cause similar signs of illness to those of haemorrhage, and yet in the one case the blood volume is seriously reduced while in the other it may be within the normal range. This gives the lie to those who state that "shock" is due to a reduced blood volume. Details of how to recognize the various states arising from injury can be found elsewhere (*Brit. med. Bull.*, 1954, vol. 10).

During World War II the opportunity arose to study the general effects of injury in a group of patients who, apart from trauma, were fit young men; in these it was found that the illness, in the commonest form of injury, was due to blood loss. Since the War the effects of blood loss have been studied extensively. Some of these researches have been collected here, but unfortunately the space in the Journal does not allow for a complete treatment of the subject. Nevertheless, much of the material should be of great interest to anaesthetists.

Brit. J. Anaesth. (1958), **30**, 450

ACUTE HYPOTENSION IN ANAESTHETIZED AND CONSCIOUS MAN

BY

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THE clinical descriptive terms "shock" and "peripheral failure" have the merit of brevity and long usage. Difficulties arise when practical measures have to be taken, for "shock" covers a large number of different mechanisms and the appropriate methods of prevention and treatment are equally diverse. There also seems to be no reason for the continued use of the term "peripheral failure" as it is commonly applied to man, for the intense constriction of skin and muscle vessels observed in some low blood pressure states is now known to be compensatory, mainly reflex, in origin.

Since 1941 when Cournand and Ranges published their paper on the Fick method in man, it has been possible to investigate the simple formula: arterial pressure $\propto$ cardiac output $\times$ total peripheral resistance. In more recent years continuous methods of recording have become generally available and allowed something to be said about events occurring over a few seconds, while the presence or absence of circulatory reflexes and the behaviour of the heart to acute filling pressure changes can be demonstrated by simple repeatable tests.

METHODS

For research purposes many methods have been used to study the circulation of anaesthetized subjects, but the simultaneous measurements of cardiac output, vascular pressures and peripheral blood flow in various parts and organs tend to leave little room for a surgeon. An attempt will be made, therefore, to examine the usefulness of some of these methods from the practical point of view.

Arterial pressure.

The standard cuff method is adequate for routine operations carrying little risk, but it is advisable to recognize its limitations. Apart from well known artefacts such as large arms causing an erroneously high measurement, the cuff method has two main defects; it is slow, and it depends on pulsation distal to the cuff. When a high pressure cuff is inflated on a limb the systolic pressure just proximal to the cuff is increased (in a dilated limb by as much as 30 mm Hg). As the cuff pressure declines, pulsations of a few mm Hg are recorded distal to the cuff and the full pulse pressure is not available until the diastolic pressure is reached. The method breaks down when mean pressure and pulse pressure are low or the peripheral vessels are so constricted as to damp out the small pulsations needed to detect the systolic level.

The auscultatory method tends to become unreliable below about 80 mm Hg and palpation below 60 mm Hg. These criticisms apply not only to the standard cuff method but to those methods which depend on a feed-back device detecting pulsation distal to a cuff and purporting to give a continuous recording of systolic pressure. The relative slowness of the method causes pressure swings over a few seconds to be neglected or misinterpreted, yet changes of arterial pressure of more than 40 mm Hg can occur with respiration in both conscious and artificially respired anaesthetized subjects. Such changes may make the assessment of pulse pressure by the cuff method totally unreliable. It will be seen that there is no short cut to direct intra-arterial pressure measurement, if all available information is required. Apart from a conservative dislike of arterial puncture, the main objection to direct measurement is expense. Monitor cathode-ray tubes or expensive pen-writers are unnecessary and are often just one more piece of equipment to go wrong. With a little practice all necessary monitoring can be done by observation of a galvanometer spot.

For those who only require a continuous pressure record occasionally, a cheap method is to use a strain gauge recording through the A-C ampli-

fier of an electrocardiogram (fig. 1). Pulse pressure changes are accurately recorded but not mean pressure changes over a few seconds owing to the short time constant. An approximate calibration of mean pressure may, however, be obtained. Arterial puncture is still, of course, necessary.

Cardiac output.

The measurement of oxygen consumption and A-V O_2 difference presents great difficulties under an anaesthetic and a dye or radio-active technique must be employed if a few records of minute output are required. In practice, however, the absolute value of the minute output is of less significance than the changes of stroke output in an individual patient. Changes in stroke output can be assessed over long or short periods from a continuous arterial pressure record. Indeed this is the only useful method at the present time. Not even the most enthusiastic workers with the ballistocardiogram have attempted to compete with the muscular tremors of a surgical team.

Central venous pressure.

Theoretically, measurement of changes in the effective filling pressure of the heart should be of great value. Practice dictates otherwise. The first complication is that intrathoracic pressure changes must be taken into consideration. Measured with a tube in the oesophagus (Dornhorst and Leathart, 1952) intrathoracic pressure is subtracted from right auricular or ventricular pressure using a differential manometer (Lee, Matthews and Sharpey-Schafer, 1954). The sensitivity of the system must be high and artefacts are correspondingly large. Indeed it is necessary to ask the anaesthetist and surgeon to cease operations if any useful measurement is to be made. The most serious difficulty, however, lies in the small magnitude of the changes to be measured. In severe surgery the concern is with falls in filling pressure from a normal or reduced level and these may amount to only a few mm Hg for large decreases in cardiac output.

As will be mentioned later, there may be more

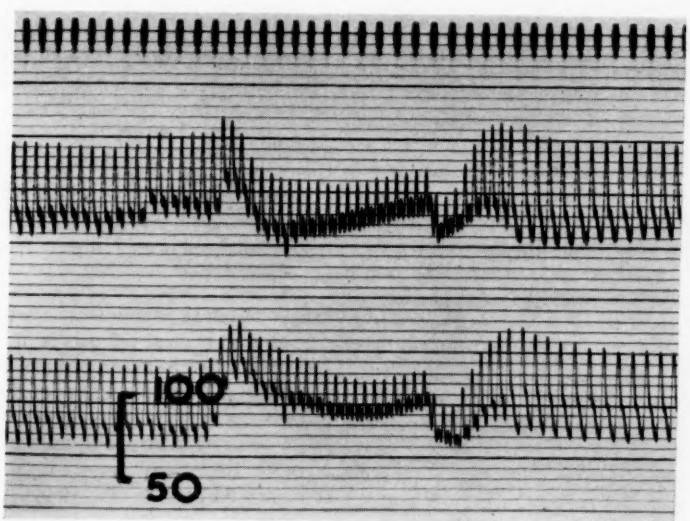

FIG. 1

Simultaneous arterial pressure curves from a subject performing the Valsalva manoeuvre. The upper curve is recorded with a strain gauge and the a–c amplifier of an electrocardiogram, the lower curve with a capacitance manometer and its d–c amplifier. Pulse pressure changes are accurately reproduced but not mean pressure changes. Time marker in seconds in this and subsequent figures.

practical value for this measurement in the post-operative period.

Resistance of peripheral vessels.

Resistance is usually calculated as the supply pressure divided by the flow to the part. In the forearm, flow can be measured with a plethysmograph and in recent years it has become essential to record arterial pressure simultaneously, particularly during rapid changes. A plethysmograph can only be used in certain postures and being bulky may obstruct the operating team. A recent method (Hayter and Sharpey-Schafer, 1958) of recording changes in vascular resistance has some advantages over plethysmography. It is simple, rapid and free from artefact. A cuff and a needle recording in a distal artery are all that are required, changes in resistance being measured by the fall of pressure after 1 sec. occlusion.

This arterial "run-off" method has been used successfully in difficult circumstances such as the dental chair (Sharpey-Schafer, Hayter and Barlow, 1958) and the human centrifuge (Howard and Garrow, 1958).

Other methods.

Electrocardiography. The electrocardiogram never offered much interpretable information and is largely unnecessary if a continuous arterial record is available. Thus not only are acute rhythm changes visible in the latter but their effects on the heart and peripheral circulation are also demonstrated.

Oximetry. The recording oximeter is at present so temperamental an instrument that only those deeply acquainted with its foibles are likely to obtain useful records.

Arterial pO_2 and pCO_2. Apart from a few special operative conditions, these measurements are likely to prove most useful in postoperative disasters, especially when respiratory function appears involved.

Finger plethysmography. This has a certain charm in the hands of a few enthusiasts. It ceases to operate when the arterial pressure becomes low.

EFFECTS OF ACUTE HAEMORRHAGE

In conscious normal subjects acute blood loss fires the faint reflex with low arterial pressure and bradycardia (fig. 2). Thus about 10 per cent faint at 500 ml, 60 per cent at 1000 ml, and a few determined experiments up to 1500 ml suggest that all normal subjects faint eventually. The hall-mark of this reflex on the efferent nervous pathway is vasodilatation of muscle vessels, though recent continuous records suggest that acute decrease in stroke or minute output may be a more important factor than was originally thought (Barcroft et al., 1944). On the afferent pathway there is some evidence that the receptors lie in the heart and the reflex is fired by large pressure transients which develop when the ventricles are contracting on a virtually empty chamber during systole.

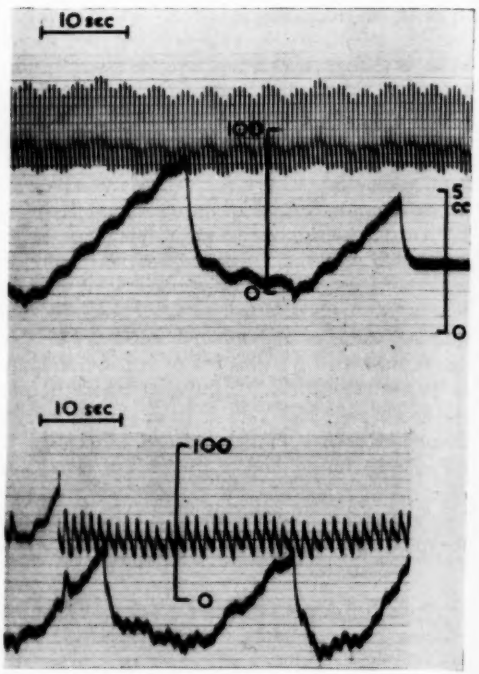

FIG. 2

Vaso-vagal fainting in a conscious supine subject. Upper record control, arterial pressure above, forearm volume below. The rate of increase of forearm volume on applying a collecting cuff is proportional to the flow. Lower record during fainting. Arterial pressure is low and forearm flow slightly increased indicating conspicuous dilatation of forearm vessels.

This reflex is abolished by general anaesthesia and it is as well that this is so, for surgeons may

not realize the extent of the effective haemorrhage that they produce. Thus "no blood loss" may be assessed at 500 ml, "a little" at 1000 ml, and "loss requiring a pint" at 1500 to 2000 ml. If the faint reflex were still present under anaesthesia few surgeons or anaesthetists would operate happily. There is one example where fainting occurs with an anaesthetic: the dental gas. But the evidence suggests that the reflex is fired by fear of this formidable situation before nitrous oxide is given (Sharpey-Schafer, Hayter and Barlow, 1958).

The effects of haemorrhage in anaesthetized man are simpler and correspond closely with much data in the experimental animal. Initially with a fall in the filling pressure of the heart and decrease in stroke output, mean arterial pressure is maintained by reflex constriction mediated through the baroceptors. Eventually cardiac output and arterial pressure fall to a low level (fig. 3). Peripheral blood flow is also conspicuously decreased (de Wardener et al., 1953).

Circulatory reflexes.

In both conscious and anaesthetized subjects changes in stroke output cause reflex constriction or dilatation. While dilatation is demonstrable after a single large beat or cough transient, 5 or 6 seconds of diminished pulse pressure are needed to cause constriction. There are a number of

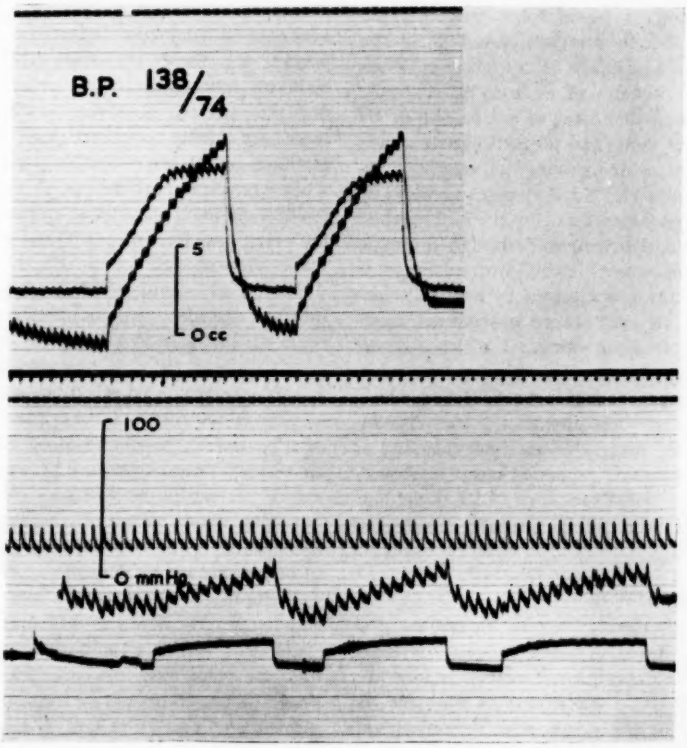

FIG. 3

Effects of 1300 ml rapid blood loss on an anaesthetized supine subject. Upper record control, forearm venous pressure above, forearm volume below. Lower record after haemorrhage. From above downwards: arterial pressure, forearm volume, forearm venous pressure. Forearm flow is greatly reduced.

mechanisms in conscious subjects causing decrease in filling pressure, stroke output and arterial pressure over a few seconds to a degree that results in syncope, before reflex constriction restores arterial pressure and consciousness. The Valsalva manoeuvre, violent coughing, and rising from the squatting position are examples.

In the anaesthetized subject artificial respiration or "squeezing the bag" is the commonest mechanism. There is a difference between a normal subject performing the Valsalva manoeuvre and raising the intrathoracic pressure in an anaesthetized paralyzed subject. For a given rise of intrathoracic pressure the circulatory effects are far greater in the latter. In the conscious subject the abdominal muscles are contracted and the effective redistribution of blood takes place in the veins of the limbs; in the paralyzed subject the abdominal vessels also act as a reservoir. Rises of intrathoracic pressure of as little as 10 to 20 mm Hg may cause decreases of stroke output by more than 50 per cent, and the subsequent reflex constriction may result in swings of arterial pressure up to 100 mm Hg. Such changes seem to be missed or wrongly interpreted by the cuff method of measuring blood pressure. Although dramatic on a continuous arterial trace, little damage is done in short routine operations by fierce squeezing of the bag. In long severe procedures, however, records have been obtained which suggest that mishandling of respiration has been an additional factor in producing dangerous low blood pressure states. In such operations, too, circulatory reflexes may disappear as time goes by, as shown by the absence of constriction or "overshoot" when the intrathoracic pressure is deliberately raised and the pulse pressure diminished over about 10 sec.

Irreversible hypotension.

Measurements during severe operative procedures lasting up to 7 hours suggest that man behaves like the experimental animal. More and more blood has to be transfused to maintain the filling pressure of the heart, which tends to fall off rapidly even though no overt haemorrhage is being caused by the surgeon, and more than 6 litres of blood are commonly used in such operations. Initially with each rapid transfusion there is a rise of stroke output and arterial pressure but eventually both remain reduced. Tests may then show that the heart itself is failing, for acute filling pressure changes (as by "squeezing the bag") produce no change in stroke output (Sharpey-Schafer, 1955). Although a higher arterial pressure may be maintained by a continuous noradrenaline infusion, experience suggests that the situation is usually beyond reclaim, for absent circulatory reflexes and respiration indicate that the nervous system is irretrievably damaged. It is in such hypotensive states in their early or later phases that the mechanisms discussed by Fine (1958) and Zweifach (1958) are most likely to prove important in man.

Postoperative hypotension.

It must be admitted that little useful data are available during the immediate postoperative period, for there are many difficulties in the elaborate investigation of severely ill patients during this period. Recovery wards and "shock" teams are mainly concerned with simple empirical methods of treatment and are rarely equipped to study complex mechanisms. A slow decline or a sudden decrease in arterial pressure is seen only too often and intense peripheral constriction may make clinical assessment of the case difficult. Thus it may be impossible to decide whether the internal jugular venous pressure is high or reduced. In these circumstances it is justifiable to pass a catheter into the great veins or auricle and at least determine whether transfusion is likely to be life-saving or fatal. An intra-arterial record can be useful in determining the state of the circulatory reflexes and the presence of heart failure or pericardial tamponade. Fulminating infection may cause reduction in filling pressure and stroke output and the heart may cease to respond to filling pressure changes.

Little has been said of the role of the peripheral venous system. Work is still in the experimental stage, but evidence is beginning to accumulate that the veins respond to reflex impulses, while slower acting humeral mechanisms probably also influence this vascular bed. It is unlikely that the veins are as passive as was once supposed and it may yet be found that changes in venous tone play an important part in the production of hypotensive states which at present are little understood.

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THE HEART IN ANOXIA AND ISCHAEMIA

BY

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IN its structure and mechanics the heart does not differ greatly from skeletal muscle (Szent-Gyorgyi, 1953). However, unlike skeletal muscle, the myocardium must undergo constant rhythmic contraction. Olson and Schwartz (1951) point out that the heart is admirably designed both structurally and biochemically for continuous aerobic work. The myocardium is three to four times as vascular as skeletal muscle and the blood flow ten to twenty times as great per unit weight of tissue. Coronary sinus blood has a very low oxygen content indicating high oxygen extraction. The oxidative enzymes, cytochrome C, cytochrome oxidase and succinic dehydrogenase are more concentrated in the heart than anywhere else in the body. Also there is a closer adjustment between energy production and energy utilization in the myocardium than in other muscles. Creatine phosphate which is usually considered as a source for reserve energy is less abundant in the myocardium than in skeletal muscles (Lipman, 1941). Recently Sarnoff et al. (1958) were unable to detect any oxygen debt incurred by the heart under physiologic work load.

It has become increasingly important to understand how this normally aerobic organ responds when deprived of its usual supply of oxygen in varied circumstances such as myocardial infarction, haemorrhagic shock and modern heart surgery. In this paper we shall discuss the local compensatory mechanisms for increasing the supply of oxygen, the metabolic changes that occur when these compensatory mechanisms do not keep pace with the demand and finally the survival of the completely ischaemic heart.

I. COMPENSATORY MECHANISMS TO MAINTAIN OXYGENATION.

When the demand of an organ for oxygen increases, the need may be met by increasing the blood flow and by increasing the amount of oxygen extracted from the available blood. The heart usually responds predominantly in the first manner (Bing and Daley, 1951; Edwards et al., 1954). In normal physiologic states oxygen utilization of the heart is almost directly proportional to the coronary blood flow although changes in cardiac output and aortic pressure may affect this relationship slightly (Braunwald et al., 1958). The increase in coronary blood flow in response to oxygen need is brought about by lowering the coronary vascular resistance. The exact stimulus for this coronary vasodilitation is unknown. It is not in response to lowered oxygen tension per se (Berne, Blackmon and Gardner, 1957), to increased concentrations of lactic acid or carbon dioxide (Hilton and Eicholtz, 1925), or to high concentration of potassium (Driscol and Berne, 1957); nor is it mediated by the adrenals or sympathetics (Hackel and Clowes, 1956).

Hackel, Goodale and Kleinerman (1954) have demonstrated in intact dogs, breathing low concentrations of oxygen, that increased oxygen extraction occurs and may play a part in maintaining myocardial oxygenation when the oxygen needs of the heart can no longer be met by increased coronary blood flow. However, in their experiments increased oxygen extraction did not take place until the arterial oxygen content had reached 8 volumes per cent. The degree to which this mechanism may be helpful is limited by the already high rate of oxygen extraction that occurs in the normal heart.

II. RESPONSE TO HYPOXIA.

When, despite compensatory mechanisms, the myocardium receives less oxygen than is necessary to maintain its normal aerobic metabolism, the oxygen tension in the myocardium falls. This fall must necessarily be accompanied by a shift in the oxidation-reduction systems towards a more reduced state. The extent to which individual

members of the electron carrier system will shift toward the reduced form will be determined by the inherent redox potential of the system in a manner reminiscent of the way the pK of a buffer system governs shifts in pH (Hewitt, 1950). Diphosphopyridine nucleotide (DPN) has the lowest potential in the carrier system. As Huckabee (1958a) has pointed out, the rates of oxidation for energy production will not be altered until DPN has been affected. When the oxidative potential has become low enough, the metabolic systems are involved; the first DPN coupled system to be reversed will be the one with a potential closest to that of DPN:$DPNH_2$, or the lactic dehydrogenase system.

(Pyruvate) + ($DPNH_2$) $\underset{\rightleftharpoons}{\text{LDH}}$ (Lactate) + (DPN)

An increase of $DPNH_2$ would, by mass action, shift the equation to the right with the production of lactate and the oxidation of DPN. Because lactate does not take part in any other equilibrium, this reaction acts as a safety valve in the presence of hypoxia, thereby permitting other metabolic oxidative systems to continue to function. Huckabee (1958a, b) has demonstrated the correspondence of the magnitude of excess lactate production and oxygen debt in the whole body. If, despite hypoxia and relatively high concentrations of $DPNH_2$ the reaction continued to the left of the equation because of excess lactate or because of diminished production or the rapid removal of pyruvate, one might expect the lactate utilization to be less normal. Such has been found to be the case. Experiments from this laboratory have shown that anoxia results in a decreased myocardial extraction ratio of lactate (Bing, 1954). Similar results have been reported in dogs breathing 5 per cent oxygen (Hackel, Goodale and Kleinerman, 1954). Extraction ratios of glucose and pyruvate also fell in these dogs and pyruvate extraction decreased markedly in dogs rendered completely anoxic. Because glucose and pyruvate have complicated alternate metabolic pathways, it is not possible to delineate individual reactions as has been done for lactate.

During haemorrhagic shock in dogs Edwards, Siegel and Bing (1954) found that the oxygen content of the blood and the pO_2 remained normal, but the coronary blood flow diminished both during the oligaemic and normovolaemic phases. As a result of failure of oxygen extraction to increase, myocardial oxygen usage declined. In the hypovolaemic phase of shock blood levels of glucose rose to high peaks, but the rise in glucose extraction was statistically not significant. Pyruvate extraction fell and negative coronary A-V differences occurred frequently. Blood lactate rose to very high levels, presumably as a result of anaerobic glycolysis elsewhere in the body. Total myocardial extraction of lactate was actually higher than during control periods, but not as high as one would have expected in a normal, fully oxygenated heart. After retransfusion to normal blood volume the myocardial extraction of lactate and pyruvate was depressed similar to that during the hypovolaemic state. Blood glucose levels fell to normal with increases in the blood volume. Myocardial glucose extraction was statistically not different from that during the control period; however, in several instances concentrations of coronary vein glucose exceeded that in arterial blood. Thus the essential changes in coronary blood flow and myocardial metabolism in haemorrhagic shock persisted during the normovolaemic phase. In both stages myocardial oxygen usage was low and the extraction of glucose, pyruvate and lactate was impaired.

III. RESPONSE TO ISCHAEMIA.

If the oxygen supply to the heart is completely interrupted, the muscle cells die unless blood flow is resumed before irreversible damage occurs.

Scattered reports have suggested that the anoxic heart may survive for long periods (see, for example, Kuliako, 1903), but the general clinical and laboratory experience has been that short periods of anoxia result in myocardial death. Blumgart, Gilligan and Schlesinger (1941) noted gross and microscopic evidence of infarction in dog hearts in which the coronary artery was occluded for 25 to 45 minutes but no evidence of infarction when the occlusion lasted less than 20 minutes. Cooley and DeBakey (1956) interrupted the coronary circulation for 31 minutes using cardiac by-pass during aortic surgery. The patient recovered. Wesolowski and his co-workers (1952) arrested coronary perfusion in dog hearts excluded from the general circulation by means of a pump-oxygenator for 30- and 60-minute periods. Only four of the thirteen animals lived more than 3

days. Webb and Howard (1957) performed similar experiments on dogs, but the coronary vessels were flushed out with Ringer's solution to prevent intravascular clotting. After 90 minutes of complete anoxia the hearts were again included in the circulation. Eleven of twelve hearts were able to sustain whole body circulation. There were no long-term survivors, however.

Recent concurrent studies in this laboratory have centred on the survival of the excitability, energy production and energy utilization of the heart (Kardesch, Hogancamp and Bing, 1958b).

A. *Survival of energy production.*

The normal heart extracts significant amounts of glucose, pyruvate, lactate, fatty acids, ketones and amino acids from the coronary arterial blood (Bing et al., 1953, 1954; Ungar et al., 1955). In the postabsorptive state the myocardium derives 70 per cent of its energy requirement from non-carbohydrate material, chiefly fatty acids (Bing et al., 1954), but the actual amounts of substrate extracted vary directly with the blood level of the substrate. Total myocardial energy production is reflected in the oxygen consumption of the heart providing glycolysis is absent.

Michal, Beuren, Hogancamp and Bing (1958) have studied the survival of energy production in the arrested dog heart. The arrested heart consumes about 25 to 35 per cent as much oxygen as does the normally beating heart (Beuren, Sparks and Bing, 1958). The heart was stopped with potassium chloride and the coronary arteries were perfused. Oxygen consumption and the myocardial extraction of its usual foodstuffs were determined. After control samples had been obtained, coronary artery perfusion was interrupted for a predetermined period of time, following which it was resumed. Oxygen consumption and the extraction of foodstuffs were again determined and these values were compared with control figures.

Results disclosed that oxygen consumption returned to control levels if the period of interruption did not exceed 2 hours (fig. 1). Longer interruption of the perfusion resulted in incomplete return to control levels. After 4 to 5 hours of anoxia the myocardium completely lost its ability to extract oxygen. Myocardial glucose extraction returned to normal even when the oxygen usage was decreased. The extraction of more glucose than could be oxidized by the oxygen taken up indicated that glucose entered metabolic pathways other than oxidative ones. Such would be the case if oxidative enzymes were more sensitive to oxygen lack than were other enzyme groups. Pyruvate extraction fell after a period of anoxia and lactate production by the heart increased even in the presence of adequate oxygen uptake.

When tissue slices were studied rather than the whole heart, oxygen uptake was found to return to only 40 per cent of control values after only 1 hour of anoxia (fig. 2). Rapid falls in oxygen consumption in tissue slices have also been reported by Webb, Saunders and Thienes (1949) and by Fuhrman, Fuhrman and Field (1950). The respiratory quotient (R.Q.) of the heart slices rose to levels above 1. There was a linear relationship between the preceding period of anoxia and the height of the R.Q. Since glucose was the substrate used in the media, the R.Q. should normally be 1. The excess carbon dioxide contributing to the high R.Q. must have originated from the action of acid on the bicarbonate buffer system of the media. These findings favour the production of lactic acid despite adequate supply of oxygen. Thus in heart slices, as in the whole heart, there is evidence for inefficiency of aerobic pathways of metabolism.

The study of the survival of myocardial enzymes after the onset of complete ischaemia is still in an early stage. Dixon (1951) points out that many essential constituents of living matter are unstable substances continually needing resynthesis. This is true of some enzymes and especially true of many coenzymes. It is the oxidative reactions that they themselves catalyze that furnish the free energy for their resynthesis and keep the enzyme-coenzyme systems in being. He reasons that the reactions may continue anaerobically if the oxygen supply is interrupted. Soon the coenzyme concentration starts to fall. If oxygen is supplied before the fall has proceeded too far, the metabolic processes will start up again and rebuild the supply of essential coenzymes. If, on the other hand, the supply of coenzyme has fallen too far, oxidative processes cannot restart and coenzyme cannot be resynthesized. Death is the result.

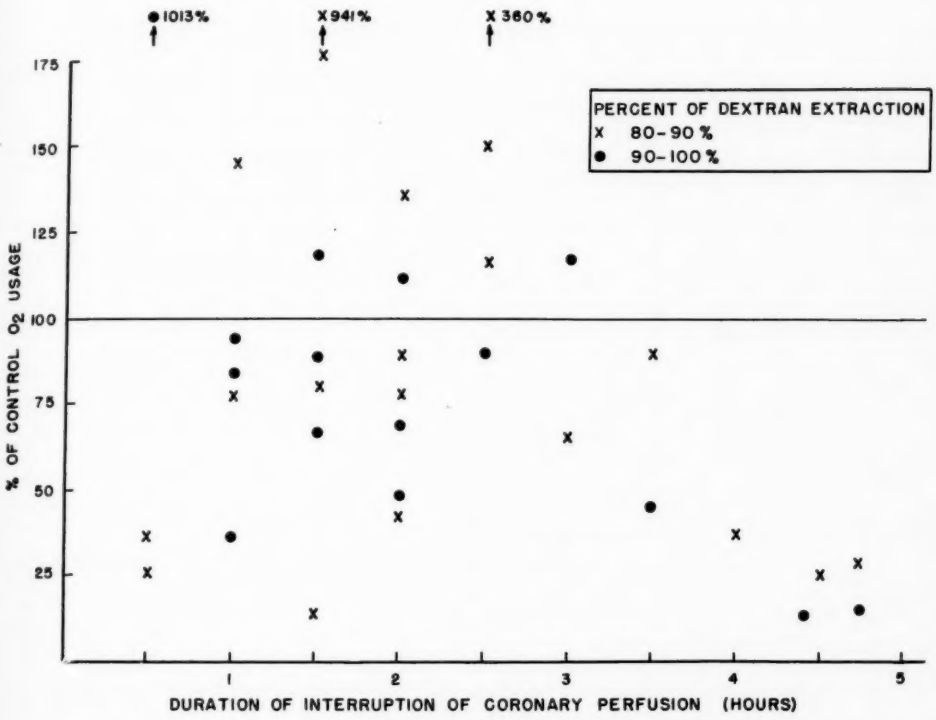

FIG. 1

The per cent of control oxygen usage of the intact dog heart is plotted against the duration of interruption of coronary perfusion. Dextran was used in the perfusion fluid to rule out mixing from extra coronary sources.

The nature of the changes in enzymatic activity with anoxia has not been established. Govier (1944) found very little destruction of DPN 1 hour after death. Two hours after coronary ligation the DPN was considerably diminished, but there was no change in the cocarboxylase (Govier, 1945). Working with tissue slices that had been incubated under anoxic conditions for 30 minutes, Bernheim and Bernheim (1944) found that the heart utilized succinic acid, indicating that the depressed oxygen uptake was not caused by damage to the succinic acid dehydrogenase or the cytochrome-cytochrome oxidase system. Lactic acid and pyruvic acid were also consumed, indicating no significant damage to lactic or pyruvic dehydrogenase or to DPN. Staining techniques have also demonstrated the resistance of succinic dehydrogenase to anoxia (Wachstein and Meisel, 1955).

B. *Survival of energy utilization.*

The energy obtained from the oxidation of foodstuffs must be transformed into mechanical energy. In the myocardium as in other muscles the energy from metabolic pathways is collected as high energy phosphates (Lipman, 1941). These high energy sources are then drawn upon as needed for mechanical work (Szent-Gyorgyi, 1953). Adenosine-triphosphate (ATP) is thought by many to be the main energy transfer agent in muscle although other high energy phosphate compounds may also play a minor part (Perry, 1956b).

Many workers using a variety of techniques

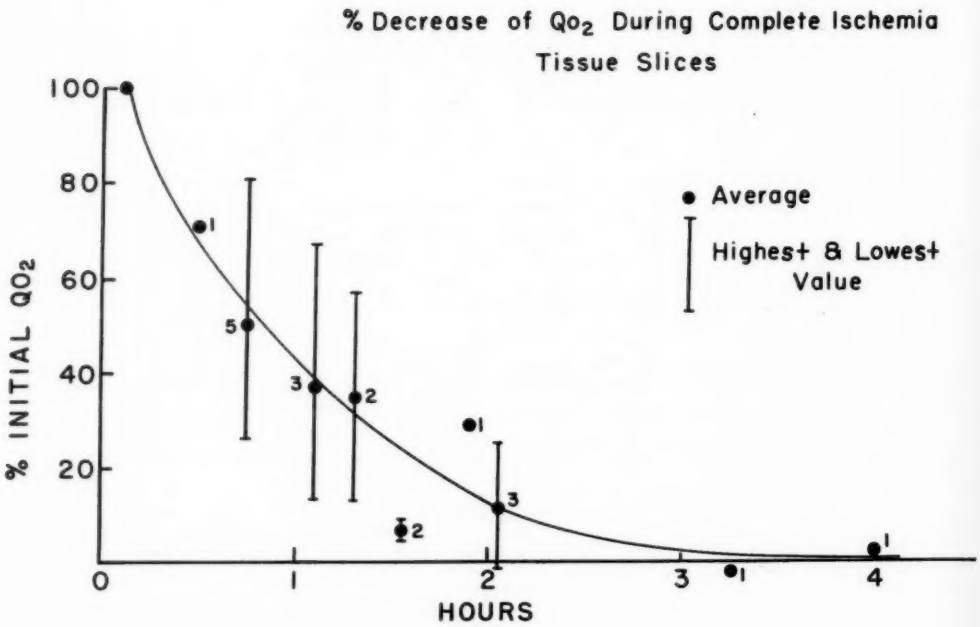

FIG. 2

Per cent of initial oxygen uptake by dog heart slices plotted against hours after death of the animal.

have deepened understanding of the chemistry and physiology of muscle contraction. Extraction techniques have shown that there are at least two contractile proteins in muscle—actin and myosin (Bailey, 1956). Szent-Gyorgyi (1952, 1953) believes that in the normal resting state actin and a myosin-ATP complex exist independently. Part of the myosin molecule (L-meromyosin) is thin and straight. This portion of the protein is kept from folding by repulsive forces between potassium ions attracted by ionized groups in close proximity along the molecule. When a wave of excitation passes this equilibrium is disturbed. Actin combines with the myosin-ATP complex. The characteristics of the myosin molecule are changed and in the presence of ATP increased pliability of the thin L-meromyosin segment occurs. The result is a collapse of this segment and shortening of the myosin molecule. ATP is broken down to ADP and inorganic phosphate during the reaction. For relaxation the heart requires ATP along with creatine phosphate (CP), magnesium and a heat stable protein (Marsh, 1952) identified as myokinase (Szent-Gyorgyi, 1956). In Szent-Gyorgyi's scheme relaxation would require a dissociation of actin and myosin and the regeneration of ATP, presumably in part at least from transfer of high energy phosphate from CP to adenosine diphosphate (ADP). There is some doubt as to the adequacy of this conceptual model (Perry, 1956a). Experiments by Mommaerts (1955) and Fleckenstein, Janke, Davies and Krebs (1954) have demonstrated that under certain conditions muscles can contract without breakdown of either ATP or CP.

H. Huxley and Hanson (1954) and A. F. Huxley and Niedergerke (1954) using morphologic studies came to conclusions that result in a somewhat different picture of muscle contraction and relaxation. They believe that actin filaments arise from either end of the sarcomere or muscle unit and that myosin filaments arise from the

middle of the sarcomere. These filaments then interdigitate. In the relaxed state the filaments slide easily along each other. During contraction this sliding is brought about by internal forces, probably by obliquely oriented cross linkages between the actin and myosin filaments. H. Huxley (1954) found no evidence for actual shortening of myosin filaments until they were crowded by extreme shortening of the sarcomeres.

Szent-Gyorgyi (1953) describes a "plasticizing" effect of ATP. After a change in muscle length has occurred, either by stretching or by shortening, the plasticizing quality allows the muscle to regain a tension almost equal to that originally held. Without this effect a muscle becomes rigid and responds to slow stretch with an increase in tension, finally tearing if the stretch proceeds too far.

This change in muscle property is exactly what happens in rigor mortis. Szent-Gyorgyi (1953) states that rigor mortis is due not only to the failure of actomyosin to dissociate and reverse muscle contraction, but also to the formation of abnormal cross linkages between different filaments. H. Huxley (1956), using low angle X-ray studies, showed well marked equatorial reflections at right angles to the long axis of muscle. In rigor these reflections are changed and secondary rods appear parallel to them. He suggested that in rigor the secondary filaments crystallize out permanently, thus rendering potentially reversible changes in the contractile proteins irreversible.

Under a wide variety of physiologic conditions stiffening of muscle after death is correlated with loss of ATP (Bate-Smith and Bendall, 1956). In the absence of oxygen, energy may be made available for resynthesis of ATP from creatine phosphate and from glycogen via anaerobic glycolysis. Rephosphorylation of ADP then may continue as long as adequate stores of glycogen and CP persist. When the stores are exhausted, ATP levels fall and dynamic resynthesis of ATP is upset. Bendall (1951) has shown that the onset of rigor mortis is more closely correlated with a decreased turnover rate of ATP than with the actual level of ATP.

After death or in complete anoxia, the pH of muscle cells falls with the production of lactic acid. Bendall (1951) points out that the initial pH at death varies the state of the muscle at that time. The end pH is dependent on the total lactic acid production which is in turn a function of the glycogen stores available at the time of death. The relationship of the onset of rigor mortis to the pH has been elucidated (Bendall, 1951). The turnover rate of ATP is affected by the pH. The maximal turnover rate is near a pH of 6.3. Hence, at this pH stores of glycogen and CP are rapidly depleted. The pH dependence curve of ATP breakdown is very similar to the myosin-ATPase activity curve and suggests a relationship with this enzymatic activity (Bate-Smith and Bendall, 1949). The breakdown of ATP is temperature-dependent. Increasing temperature shortens the delay period of rigor mortis (Bate-Smith and Bendall, 1949).

When one turns from skeletal muscle to heart muscle, one finds that rigor mortis occurs much more rapidly (Lawrie, 1953). This rapid onset of rigor is in keeping with the low CP supply of heart muscle (Fawaz and Hawa, 1953). Being well adapted for continuous aerobic work, the heart has little stored energy.

The survival of contractile proteins of human heart muscle after death has been studied by Kako and Bing (1958). Actomyosin bands were obtained from muscle homogenates prepared at varying intervals after death. Properly prepared actomyosin bands in a suitable ionic environment will contract on the addition of ATP. The contraction of actomyosin bands from normal hearts is influenced by the ionic concentration and the load, but, when these factors are constant, the results expressed as per cent shortening do not vary greatly. There is no significant difference in the response of actomyosin bands prepared immediately after death to bands prepared up to 6 hours after death (Kardesch, Hogancamp and Bing, 1958).

C. *Survival of myocardial excitability.*

In order to function, the heart must undergo rhythmic contraction and relaxation. This repetitive cycle is triggered by changes in potential at the cell membrane. The ability of the myocardial cell to respond to stimuli with change of membrane potential and contraction is termed excitability. In the heart a new contraction is dependent on the spontaneous initiation of action potentials by the pacemaker.

Brooks, Hoffman, Suckling and Orias (1955)

review concepts of the cell membrane and the mechanism by which action potentials arise. A brief conceptual framework borrowed largely from Hodgkin (1951) will be reviewed here to aid in considering factors important in survival of the heart. The cell membrane may be considered as a semipermeable membrane that greatly restricts movement of sodium ions and to a lesser extent hinders passage of potassium ions. Inside the cell is an active pump which extrudes Na+. The loss of positively charged Na+ disturbs the electroneutrality. Potassium ions then diffuse in, driven against the concentration gradient by the potential gradient. An equilibrium is eventually reached with a relatively high concentration of K+ and a low concentration of Na+ in the cell. At this equilibrium there is an electrical potential of from 80 to 90 mV across the cell membrane so that the outside of the cell is positive to the inside. The magnitude of this potential depends on the ratio of the K+ outside the cell to the K+ inside the cell.

When the membrane potential is lowered by a suitable stimulus, the permeability to sodium increases. A rapid influx of sodium is brought about by both the concentration and potential gradients. The influx of Na+ is sufficient to neutralize the charge across the cell membrane. In fact, there is a "positive overshoot" that reverses the resting polarity. These changes account for the rapid depolarization phase found when unicellular action potentials are obtained (fig. 3A). At the end of this phase, the membrane again becomes impermeable to sodium and more permeable to K+. K+ then diffuses out of the cell until the equilibrium between the potential gradient and the concentration gradient is restored. The repolarization phase is much slower than the phase of depolarization. At the end of the depolarization-repolarization cycle the cell is left with a small quantity of excess sodium that is removed during the resting phase by the Na+ pump. This conceptualization overlooks the fact that considerable evidence can be marshalled in favour of anactive K+ transport as well (Weidmann, 1957).

Much of this knowledge has been obtained in recent years from a technique developed by Ling and Gerard (1949a) in which a microelectrode is placed in a single myocardial cell to record uni-

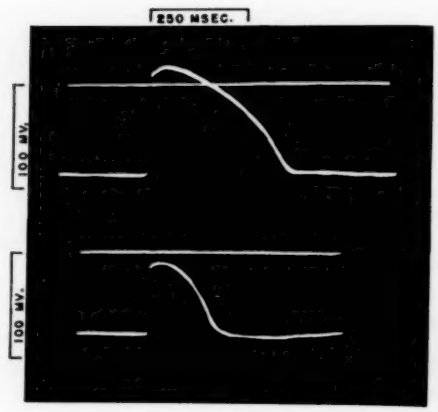

FIG. 3

(A) Normal unicellular action potential. Rapid phase of depolarization appears as a gap in photograph. Top horizontal line is zero potential.

(B) Unicellular action potential during anoxia. Note incomplete depolarization and rapid repolarization.

cellular action potentials. Recently a modification of the technique has been used in this laboratory to study the effect of complete ischaemia on the intracellular electrical activity in the left ventricular muscle of rabbits and dogs (Kardesch, Hogancamp and Bing, 1958a). The hearts were perfused and normal ventricular action potentials were obtained. Following a control period the hearts were rendered anoxic. Soon a shortening of the duration of the action potential was noted, suggesting a more rapid influx of K+ during repolarization. There was a progressive loss in the height of the action potentials. After an average of 13 minutes of complete ischaemia the membrane no longer completely depolarized (fig. 3B). After 20 minutes the action potential ceased entirely. At this time the resting membrane potential averaged only 65 per cent of that obtained with full oxygenation. Usually, an action potential can be obtained only if the resting membrane potential is sufficiently high. Weidmann (1957) has shown that if the membrane potential of an exhausted kid Purkinje fibre is raised to normal levels electrically, the ability to respond with an action potential is restored. As the action potential declined during anoxia, the rate and strength of muscle contraction also decreased (Kardesch,

Hogancamp and Bing, 1958a). If the hearts were reperfused after 10 minutes of standstill, the action potentials reappeared and returned rapidly to normal. Repeated episodes of ischaemia over a short time span caused increasingly rapid loss of the action potential.

Similar results have been obtained in the rat atria by Webb and Hollander (1956) and in the cat papillary muscle by Trautwein and Dudel (1956). It seems possible to explain inability to maintain the resting potential in anoxia by a failure of a Na+ pump or a Na+ − K+ pump.

Webb and Hollander (1956) found that 2, 4-dinitrophenol (DNP), an uncoupler of oxidative phosphorylation, affected the atrium in a fashion almost identical to that of anoxia. This suggests that decline of ATP levels may be related to the effects of both DNP and anoxia. Furthermore, Greiner (1952) has shown that decline in force of contraction in electrically stimulated anoxia cat papillary muscles is accompanied by a fall in ATP. In view of the work cited previously one would expect the force of contraction to be correlated with the action potential. Ling and Gerard (1949b) were able to demonstrate that loss of membrane potential paralleled the loss of creatine phosphate and the development of rigor mortis in frog sartorii that had been rendered anoxic or poisoned with iodoacetate.

The simultaneous occurrence of these changes may be fortuitous; however, the movement of ions against concentration and electrical gradients requires energy and is markedly reduced in the rat ventricle by anoxia (Hercus, McDowall and Mendel, 1955), and by metabolic inhibitors in the giant squid axone (Hodgkin and Keynes, 1955). High energy phosphates are a logical source of energy to maintain membrane potential.

To summarize the studies on survival: the completely anoxic heart will continue to function as a pump only as long as the resting membrane potential remains sufficiently high and action potentials are generated and propagated. Action potentials decline and disappear over about 20 minutes of complete ischaemia. At this time neither the metabolic processes nor the contractile proteins are irreversibly damaged.

Myocardial anoxia and ischaemia are important in a variety of clinical entities such as myocardial infarction and haemorrhagic shock. Among today's pressing problems are the determination of safe periods of myocardial ischaemia during surgery and the delineation of the factors that affect the duration of these periods. While much of the work cited above is not yet clinically applicable and much remains to be done, better understanding of the pathologic physiology and biochemistry of the heart must of necessity lead to improved clinical care.

ACKNOWLEDGMENTS

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MICROCIRCULATORY DERANGEMENTS AS A BASIS FOR THE LETHAL MANIFESTATIONS OF EXPERIMENTAL SHOCK*

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As the shock syndrome progresses towards a lethal outcome, it initiates changes which become increasingly difficult to reverse by known therapeutic measures. Most of our information concerning the breakdown of circulatory homeostasis has been obtained by using graded haemorrhage to produce carefully controlled hypotension, which, when sufficiently protracted, becomes irreversible to blood replacement measures. Although the basic defect has long been known to be a derangement of the peripheral circulation, no agreement has been reached on the actual mechanism responsible for the fatal collapse of the circulation. A seemingly endless array of theories have been advanced, ranging from the toxic and histamine concept (Moon, 1944), excessive vasoconstriction (Parsons and Phemister, 1930), adrenocortical deficiency (Swingle et al., 1944), and general exhaustion of key metabolic processes (Wilhelmi and Long, 1948), to the disruptive action of particular vaso-active agents arising in ischaemic muscle, liver, kidney, or adrenals (Green and Stoner, 1950). During the past few years, renewed interest in vasotoxic agents of bacterial origin during shock (Fine et al., 1952) has led to an intensive study of bodily defence mechanisms in structures, such as the liver and intestinal tract. Since each of the proposed concepts stems from experiments on a particular form of shock, we have no satisfactory evidence that any of these mechanisms represent the critical lesion common to different types of shock, if indeed such actually exist.

In its simplest terms, "shock" designates a collapse of the peripheral circulation arising out of a discrepancy between the volume of blood in active circulation and the capacity of the vascular tree. Under normal conditions, a precisely controlled relationship exists between the amount of blood kept in circulation and the size of the vascular bed in which it is contained. Circulatory insufficiency can arise when either the volume of the blood or the size of its surrounding vascular envelope becomes disproportionately altered with respect to one another. Thus, two fundamentally different disturbances contribute to the development of an unbalanced haemodynamic state. On the one hand, are factors such as haemorrhage, or increased capillary permeability, which reduce the circulating blood volume directly. On the other hand, are factors which interfere with the vasomotor control of the blood vessels, and unduly increase the size of the vascular bed. Thus, both extremes of vascular behaviour can be involved. However, only under exceptional circumstances is the collapse of the circulation attributable exclusively to one of these mechanisms, the majority of shock states involving a combination of different factors.

Historical Evolution of Current Concepts.

A toxic origin of shock was favoured by early workers, chiefly because the lethal course of the syndrome was first recognized in conditions with a traumatic background. Since considerable tissue damage was usually involved, it was assumed that toxins arising in the injured site were released into the circulation. The ensuing vasodilatation and capillary damage then progressed to the extent that an effective peripheral blood flow could no longer be maintained (Cannon, 1923). Excessive vasoconstriction (Remington et al., 1950) was also recognized as an important circumstance contributing to the fatal collapse. Suspicion was directed towards both overactivity

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† Established Investigator, American Heart Association.

of the sympathetic nervous system and hypersensitivity resulting from the release of tissue mediators. Following World War II, with the application of techniques for measuring blood volume, most forms of shock were shown to be associated with a serious reduction in circulating blood volume (Blalock, 1931). This in turn resulted in the use of graded haemorrhage as the method of choice for the experimental study of shock.

Comparison of haemorrhagic and traumatic shock led workers to distinguish between initiating as opposed to sustaining factors (Wiggers, 1942). Loss of fluid from the circulation was shown to be the most important factor initiating the downward course of the syndrome encountered in man. Our analysis of the shock syndrome can, therefore, best be begun by considering the circulatory readjustments of uncomplicated haemorrhage.

General Readjustments to Blood Loss.

The ensuing hypotension sets off a train of events designed to compensate for this imbalance. Phenomena such as cardiac acceleration, peripheral vasoconstriction, redistribution of blood, and haemodilution, are familiar aspects of this reaction. The earliest circulatory manifestation of oligaemia is an inadequate return of blood from the peripheral vessels to the heart. The inability of this organ to maintain an effective cardiac output and blood pressure in turn leads to a widespread peripheral vasoconstriction, presumably as a means of accommodating the capacity of the vascular bed to the diminished amount of blood in actual circulation. The net result is a compensatory situation in which the blood pressure is maintained at the expense of the blood flow to the tissues.

Homeostatic readjustments at this stage provide an important clue to the ensuing pattern of vascular activity. In essence, the primary purpose of the cardiovascular system is to supply the tissues with adequate amounts of oxygen and nutritive materials. With the loss of blood, the peripheral flow in many regions is reduced below the point where oxidative tissue metabolism can be effectively carried out. In this situation, the relative autonomy of the terminal vascular bed becomes the dominant factor and gives rise to changes antagonistic to the initial compensatory readjustments. Significantly enough, the longer this stage of the syndrome is allowed to progress, the more refractory to fluid replacement therapy the situation becomes.

The animal continues to deteriorate despite blood replacement and fatal circulatory collapse ensues. Since there was no obvious source of a toxic factor under these experimental conditions, the precise alterations responsible for the irreversible trend were at first only poorly understood. It was not until direct observational studies were carried out on the microcirculation that a clear picture emerged of the vascular sequelae which accompany severe shock.

Microcirculation Following Haemorrhage.

The microcirculation shows two discrete phases of behaviour in response to both haemorrhage and trauma (Zweifach et al., 1944). Initially, the small blood vessels go through a phase of increased vasomotor activity, coincident with a heightened sensitivity and the selective restriction of blood flow to the most central, direct channels. Provided that the blood pressure does not fall below critical levels, this type of tissue perfusion sustains aerobic metabolism and the animal is readily restored to normal by blood replacement.

Humoral agents are conceded to be the most important mediators of the compensatory readjustment within the tissues proper. Among the mechanisms reported to be involved in the heightened vasomotor activity of the terminal vascular bed are the discharge of adrenal corticosteroids (Fritz and Levine, 1951), renal vasotropic principles, such as angiotonin and VEM (Hamilton and Collins, 1944), and adrenaline or noradrenaline (Freeman et al., 1938). When the hypotension persists for several hours or more, the initial pattern of response is gradually replaced by a decompensatory tendency, which becomes manifest by a loss of the ischaemic, restricted blood flow, hyporeactivity of the muscular elements, and venous stagnation, often to the point of complete stasis. Irreversibility is uniformly associated with the full quota of decompensatory activities.

Vascular decompensation exhibits the following stigmata: (1) the progressive sequestration or trapping of blood from the active circulation; (2) a considerable fall in oxygen tension in the tissue

proper; (3) a steadily rising haematocrit; (4) an inability to sustain hypotensive blood pressure levels without continuous blood replacement; (5) the appearance of vasotoxic or inhibitory principles in the bloodstream; (6) a gradual loss of reactivity in the muscular arterioles and precapillary sphincters in visceral tissues; (7) the failure of blood transfusion to improve the microcirculation except for a short period; (8) laboured, diaphragmatic respiration followed by (9) respiratory arrest, presumably of central origin; (10) cardiac arrhythmia and arrest.

The efficacy of blood replacement measures is reflected by their ability to restore the microcirculation in visceral tissues (Zweifach, 1950). Thus, under conditions leading to irreversibility, the infusion of blood or blood substitutes results in a transient, mechanical improvement of blood flow through the capillary bed, with the added blood serving to distend the atonic arterioles and venules. In animals in which transfusion is successful, the muscular arterioles and venules resume their normal tonic appearance and spontaneous vasomotor activity is restored shortly thereafter.

The basic importance of the functional state of the microcirculation with respect to the ultimate outcome, can best be illustrated by experiments in which increasingly severe episodes of haemorrhage were used to induce shock (Zweifach et al., 1944). Three categories of peripheral circulatory collapse could be induced.

The effects of acute, massive loss of blood are represented by a syndrome in which the capillary bed as an organic unit remains unimpaired. Collapse of the circulation was a direct consequence of excessive vasoconstriction of the large blood vessels and the mechanical failure of blood to reach the tissues. This condition is readily reversed by blood replacement measures.

A second or intermediate type of shock can be obtained with graded haemorrhage. By this procedure, animals were maintained in a given state of hypotension for selected periods. The initial compensatory changes characteristic of blood loss *per se*, are progressively lost and replaced by decompensatory alterations. Blood, trapped in the capillary bed and in the small veins, serves to intensify the already severely reduced blood volume. With time, vascular decompensation predominates, coincident with the onset of irreversibility.

A third, or toxic, type of shock can be obtained regularly by superimposing the deleterious effects of anaesthetic agents, such as ether or pentobarbital, bacterial products, adrenal insufficiency, etc. In these instances, the initial compensatory responses of the peripheral vascular bed are only poorly developed and much less effective. Evidence of endothelial pathology appears in visceral tissues, coincident with stasis and haemoconcentration. This form of shock is uniformly refractory to blood replacement measures.

Decompensatory Mechanisms.

The theories advanced to explain the deterioration of peripheral vascular homeostasis deal with almost every conceivable aspect of pathophysiology. We have adopted the premise that a particular set of circumstances could be shown to be causally related to the shock sequelae only if it reproduced, or contributed to some aspect of the basic pattern of peripheral vascular behaviour.

Under normal circumstances, tissue homeostasis is achieved through the operation of regulatory mechanisms intrinsic to the terminal vascular bed and acting independently of the large blood vessels. Local changes in blood flow are obtained by the liberation of chemical mediators either in the general parenchymal tissue, or in specific cell types in the vicinity of the small blood vessels. These agents produce their effects by augmenting or diminishing the tone of the muscular arterioles and their precapillary branches through one of several mechanisms—modifying the inactivation of constrictor or dilator principles, variations in the reactivity and sensitivity of the muscular vessels to stimuli, and shifts in intracellular electrolytes (Zweifach, 1949).

Regional differences in the extent and degree of vasoconstriction during circulatory stress can be accounted for by differences in sympathetic innervation, by the pattern of vascular distribution, by interanastomoses between arterial and venous vessels, and by peculiarities in the structural make-up of the capillary bed itself.

When more extensive areas are involved, neurogenic mechanisms of the antidromic type are activated. Essentially, this type of regulation appears to guard against undue fluctuations in the

circulation of the tissue proper by interfering with the centrally induced constrictor tone of the large arterioles.

Under conditions of moderate hypotension, the operation of peripheral homoeostatic mechanisms is still adequate to distribute the blood commensurate with the aerobic requirements of tissue metabolism. When the hypotension is protracted and severe, however, these mechanisms become ineffective. Arterial and venous constriction has now progressed to such an extent that changes distal to these vessels cannot ensure an effective distribution of blood through the capillary vessels (table I).

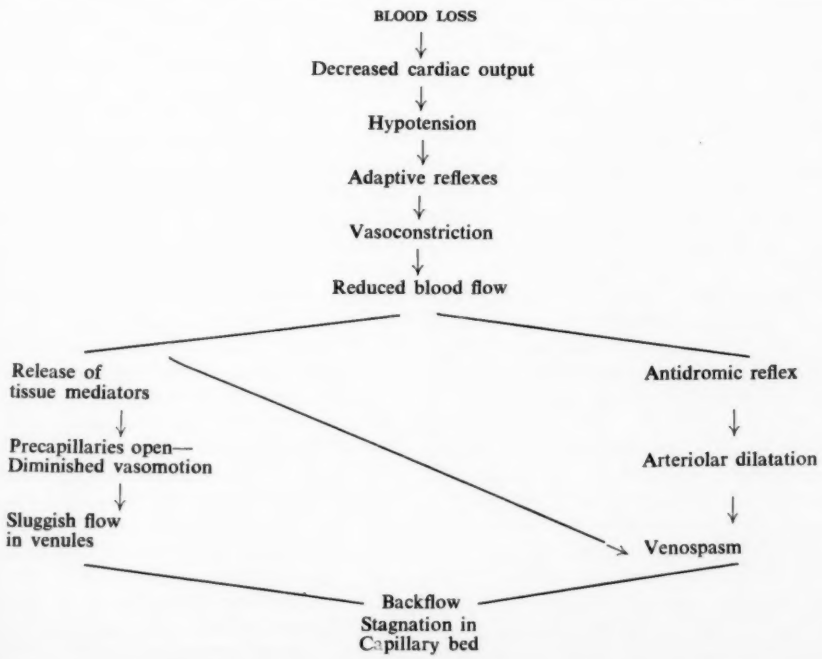
Two organs which are especially vulnerable to the deficient circulation during haemorrhagic hypotension are the liver and the small intestine. Since the liver is dependent in large part upon the portal vein for oxygen, it becomes hypoxic relatively early in shock due to a marked drop in the oxygen tension of the portal vein blood and a sharply reduced arterial supply by way of the hepatic artery. The bowel shows extensive venous constriction, which together with the interanastomosing character of the small arteries and veins, results in the early appearance of stagnation and capillary stasis.

Hepato-renal Principles.

Since the terminal vascular bed is known to be susceptible to vaso-active agents, a search was made for blood-borne principles during the separate phases of the shock syndrome. The rat mesoappendix bio-assay technique (Zweifach, 1948) was developed, utilizing the response of the same set of blood vessels in the test animal as in the

TABLE I

Readjustments of the Microcirculation following lethal graded Haemorrhage.



shocked donor from which the samples were taken. Serial blood samples revealed the presence of vaso-excitatory principles (VEM) during the early phases of the shock reaction, and the gradual appearance of a factor (VDM) during deep shock which interfered with the vasoconstrictor activities of adrenaline and noradrenaline. An attempt was then made by *in vitro* incubation experiments and tissue extraction procedures to determine the tissue origins of these vaso-active principles. Although a factor originating in the ischaemic kidney was shown to be responsible for the major portion of the vaso-excitatory activity of the blood (Chambers and Zweifach, 1947), it has not been possible to determine whether the biological properties of the samples were due to a single chemical entity. More conclusive information was obtained concerning the nature and mode of inactivation of the adrenaline inhibitory principle. Severe hypotension was associated with the accumulation in the liver and subsequent release into the bloodstream of an iron-bearing protein, ferritin (Shorr et al., 1951). The vaso-inhibitory properties of ferritin were found to be related to the reduction of S-S linkages to a free -SH form, during which process iron was released (see table II). It was postulated that ferric iron, when incorporated into an appropriate chelator, formed a substance of the Cytochrome C type, catalyzing the oxidation of adrenaline. Recent reports by Green et al. (1956) indicate that the reduction of ferritin is related to the enhanced purine metabolism during shock, through an interaction with xanthine oxidase (table II).

Hepato-renal factors of this type were later shown to be present in a variety of experimental conditions, and in disease states in man associated with impaired liver and kidney circulation (Shorr, 1954–55). These studies led the Shorr group to postulate that the VDM and VEM systems in the liver and kidney represented opposite components of a homeostatic mechanism for the regulation of peripheral blood flow (Shorr et al., 1945).

Although highly provocative, the fact that appropriate circulatory disturbances appear regularly in the mesentery, coincident with representative blood-borne agents, does not by itself constitute proof that the microcirculatory phenomena were related causally to the irreversible course of the shock syndrome. It is unrealistic *a priori* to assign a uniform toxic function to blood-borne factors, in view of the diverse responses elicited by vaso-active agents in different tissues. A more reasonable explanation would be that the formation of such principles is a reflection of their primary function as local mediators of vascular activity, and that their overflow into the circulation does not imply a systemic function. Studies on five major tissues indicate that identical changes in the direction of both hypo- and hyper-reactivity can be produced on a purely local scale within each tissue (Zweifach and Metz, 1955). We may therefore be dealing in the shock syndrome with regional reactions, each brought into play by separate metabolic and neurogenic factors. On this basis, decompensation would not necessarily develop as the consequence of a single set of humoral factors.

Actually, there is no evidence of a generalized vascular decompensation (see table I). Little or no damage to the vessels in the skin and skeletal muscle can be detected following uncomplicated haemorrhage—despite the fact that the circulation through these tissues is severely curtailed and remains highly ischaemic throughout the syndrome. The blood flow through the kidney is reduced almost to the point of complete shut-down without evidence of decompensatory changes during the progression of irreversibility. The adrenals are congested and swollen, but on the basis of histochemical studies (Zweifach et al., 1953) do not appear to have lost their secretory capacity. Visceral structures, such as the bowel and liver, are the principal sites of venous congestion and loss of vascular tone. In animals with irreversible hypotension, the small blood vessels of the bowel show an even further inhibition of tone and reactivity after blood replacement.

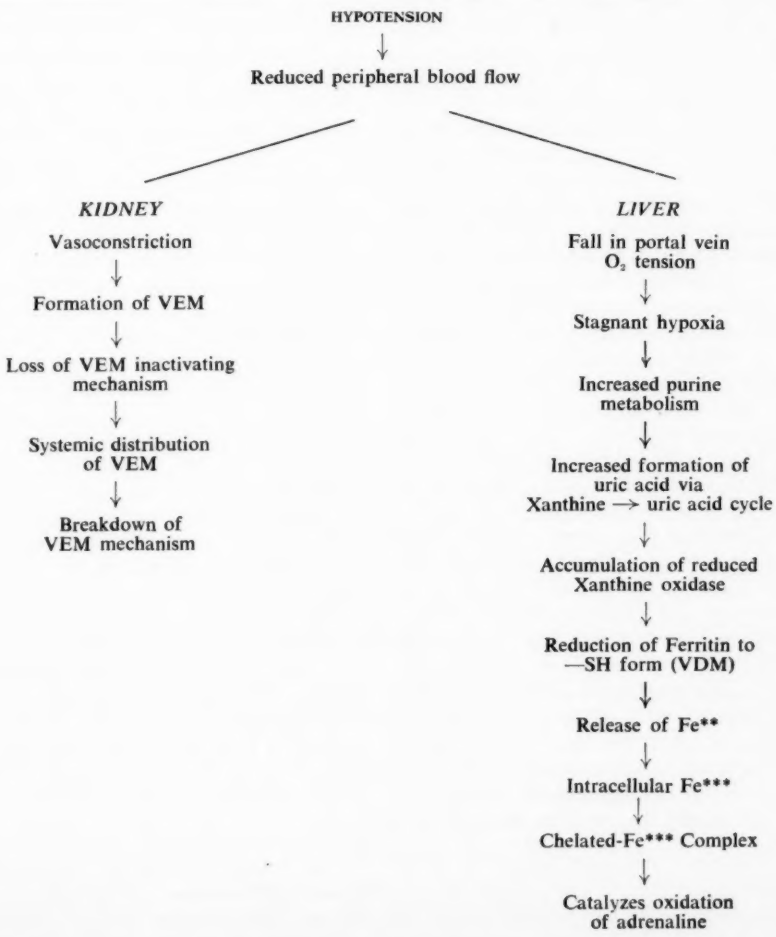
Observational studies carried out on the wall of the bowel provide visual evidence of the atonic state of the microcirculation during the irreversible phase of the syndrome (Baez, 1955). Continuous measurements of blood flow through the liver are difficult to obtain, and have not been sufficiently revealing either to support or to disprove the importance of particular toxic factors. The terminal vascular bed in the liver has a highly specialized structural organization, with no obvious arterial system of branching precapillary sphincters and thoroughfare channels. Recent

work with bacterial endotoxins (Weil and MacLean, 1956) suggests that the hepatic congestion and sequestration during the latter phases of the shock syndrome are the result of venous constriction and an increased resistance to the outflow of blood from the liver.

Are we justified in assuming that the vasotoxic manifestations of the shock syndrome are directly related to the catechol amines, adrenaline and noradrenaline? A good deal of corroborative evidence supports such a relationship. The decompensatory trend in the microcirculation was originally recognized on the basis of the altered attitude of the small blood vessels to adrenaline and noradrenaline. Bacterial endotoxins, another of the proposed toxic factors, produce marked

TABLE II

Schema of Hepato-renal Homeostasis during Haemorrhagic Shock.



distortions in the pattern of response to adrenaline (Zweifach et al., 1956), not unlike those seen in traumatic and haemorrhagic shock. The infusion of adrenaline or noradrenaline leads to peripheral circulatory collapse characterized by visceral congestion and pathology (Erlanger and Gasser, 1919). Unfortunately, our knowledge of the precise role of adrenaline and noradrenaline in peripheral vascular homeostasis is too incomplete to allow an objective evaluation of the relationship of these amines to the shock syndrome.

Several investigators (Frank et al., 1952a) have pointed out that they were unable to induce circulatory collapse by the infusion of ferritin into normal animals. This is not an unsurmountable criticism, since the postulated vasotoxic effects of ferritin occur during shock when liver metabolism is impaired, the circulation through the intestine is markedly reduced, and general tissue hypoxia prevails.

Although microcirculatory and bio-assay studies have answered a great many problems, they have left unanswered others which are difficult to reconcile with the concepts thus far proposed. The shock syndrome is primarily characterized by pathological changes in the liver and intestinal tract, with ancillary changes in the adrenals, lymphoid structure, and kidney. To what can we attribute the seemingly selective pathology induced by these vaso-active principles in the liver and bowel and not in other tissues? The predilection to damage in these structures would seem to be the result of a combination of circumstances. The reduced flow serves to initiate metabolic changes, which in turn exacerbate the circulatory defect in that area and thereby to set up a vicious cycle. Early in the syndrome, restoration of blood volume and blood pressure checks the self-destructive tendency. Later, the metabolic and vascular changes progress to the point where the mechanical improvement of blood flow is by itself inadequate. On this basis, the systemic effects of a circulating toxin would be limited to those areas in which local changes have predisposed or sensitized the vascular bed to such substances.

Bacterial Factor.

At about the time the hepato-renal concept of shock was advanced, another group of investigators focused attention on the changes in the bowel (Jacob et al., 1954). Fine and co-workers concluded that the decisive element during shock was the hypoxia of the bowel which in turn led to bacteraemia and a loss in the vitality of the intestinal wall sufficient to allow bacterial products to enter the circulation. The bacteraemia concept was originally formulated on the basis of studies in laboratory animals pretreated orally with various antibiotics, a procedure which made them resistant to normally lethal episodes of haemorrhagic shock (Frank et al., 1952b). Corroborative studies showed that animals, subjected to the stress of severe, unrelieved hypotension, no longer effectively cleared bacteria from the bloodstream (Schweinburg et al., 1954), were inordinately sensitive to the toxic and lethal effects of bacteria and their endotoxins (Schweinburg and Fine, 1955), and developed a profound fall in the blood levels of properdin, a naturally occurring antibacterial factor (Frank et al., 1955). Since an equivalent protective action could be induced with antibiotics such as neomycin, which were not absorbed from the intestinal tract, these investigators felt that the toxic element was of enteric origin. Subsequently, on the assumption that bacterial endotoxins are the toxic elements, they prepared extracts of blood by procedures established for the isolation of endotoxins from gram-negative bacteria and found that the blood of shocked animals yielded a product which exhibited many of the properties of bacterial endotoxins (Schweinburg et al., 1957).

Other evidence points to the intestinal tract as an important element in the evolution of the shock reaction without defining the responsible mechanisms. The lethal outcome of graded haemorrhage could be circumvented by perfusing the small intestine with arterial blood (Lillehei, 1956). Selkurt (1958) is also of the opinion that the gut liberates a toxic factor during shock. He reached this conclusion on the basis of *in situ* measurements of blood pressure and flow in the portal and hepatic veins.

Microcirculatory Effects of Endotoxins.

Our interest in this area was stimulated by several circumstances. Inasmuch as many points of resemblance can be found between the shock induced by bacterial products and that resulting

from traumatic and haemorrhagic injury, we felt that an intensive study of the vascular effects of bacterial endotoxins would serve as a useful frame of reference for comparing different forms of shock. Although we have been able to compile substantial support for the identity of haemorrhagic, traumatic, and endotoxin shock (Zweifach and Thomas, 1957), the evidence is for the most part circumstantial. One cannot overlook the possibility that the syndromes induced by bacterial factors and protracted haemorrhage or traumatic injury may be identical only with respect to the final vaso-active elements involved.

Thomas (1956), following the lead of Delaunay and Boquet (1948), showed that a prominent feature of the reaction to bacterial endotoxins was an alteration in the response of vascular smooth muscle to pressor amines, such as adrenaline and noradrenaline. Our own studies (Zweifach, 1956) revealed that, as in the case of haemorrhagic shock, endotoxaemia was associated with a biphasic derangement of vascular reactivity, consisting of an initial stage of increased responsiveness to adrenaline, and a terminal stage in which the muscular vessels no longer responded effectively to stimulation with adrenaline (table III). There were, however, significant differences, among them an extraordinary hypersensitivity of the muscular venules and small veins during endotoxaemia, and a tendency toward extensive capillary damage. These differences may well be quantitative in nature, since the initial phases of the traumatic and haemorrhagic shock syndromes involve blood volume and neurogenic factors, not encountered until much later in endotoxaemic shock after vascular damage has been inflicted. In conventional shock, endotoxaemia undoubtedly represents a secondary factor which is superimposed on to an already existing hypotension and reduced blood flow. Its potential pathological manifestations, therefore, do not develop to the same extent as in shock induced by bacterial extracts alone.

Shock in Germ-free Rats.

Smiddy and Fine (1958) assume that the endotoxaemic factor, which they can prepare from the blood of shocked animals, is derived primarily from the multiplication of gram-negative bacteria in the intestinal tract. More recently, Landy and Shear (1957) have suggested that tissue polysaccharide complexes may be released during injury and be responsible for the pathological manifestations of the shock syndrome, rather than endotoxins from enteric sources exclusively.

The evidence dealing with bacterial endotoxins

TABLE III

Circulatory Changes in Endotoxaemia and Haemorrhagic Shock in the Rat.

Vessels in mesentery	Lethal endotoxin	Irreversible shock
Arteries	Constricted	Constricted
Arterioles		
Tone	Decreased	Decreased
Reactivity*	Subnormal	Subnormal
Vasomotion	Suppressed	Absent
Capillaries		
Flow	Plethoric, sluggish	Ischaemic
Wall	Petechial haemorrhage	No effect
Venules		
Tone	Increased	Atonic
Reactivity*	Hyper	Hypo
Veins	Distended	Distended

* Response to typical application of adrenaline.

Endotoxin extract of *E. coli*, 3.0 mg i.p.

Irreversible shock—terminal stage after blood pressure for 3 hours at 35 mm Hg.

is so convincing that one is tempted to accept the fundamental importance of bacterial products, either directly or in the form of hypersensitivity, to the evolution of irreversible shock. However, far too many experimental observations cannot readily be explained on this basis. It is apparent that we do not as yet have sufficient information to permit us to arrange the available facts in their proper perspective.

Experiments with germ-free rats present perhaps the single outstanding area of disagreement with the bacterial concept of shock. Animals reared under germ-free conditions would appear to provide ideal experimental subjects for testing the validity of the bacterial thesis. Haemorrhagic shock was induced under sterile precautions in rats which for two to six generations had been reared at the Lobund Institute in a bacteria-free environment (Zweifach et al., 1958). If one were to interpret literally the basic premises of the bacterial concept, these animals should be as resistant to shock as were animals treated with antibiotics. We found, on the contrary, that irreversible shock could be produced by haemorrhage in germ-free rats as regularly and under the same conditions as in ordinary laboratory animals. No differences could be demonstrated between the response of the two groups of animals. Until some other explanation is available, the findings must be interpreted as indicating that bacteria or bacterial products are not the primary aetiologic factor in the pathogenesis of shock.

Two alternative explanations can be used to account for the seeming contradiction in the near-identity of the shock syndrome in the germ-free and in the conventional laboratory animals. Attention has been drawn to the fact that the germ-free animals probably receive bacterial endotoxins in their food and that this might be sufficient to account for the subsequent deterioration of the vascular system. According to this explanation, the hypoxia in the bowel would break down the tissue barrier, which under normal circumstances prevents the systemic dissemination of bacterial products. This suggestion is open to doubt, since many of the germ-free animals in the shock series were fed a semi-synthetic diet in which there could not be significant amounts of endotoxin. Landy and Shear (1957) have proposed that the toxic factor in germ-free animals may be the liberation of tissue polysaccharides. This contingency is, of course, purely speculative and needs to be substantiated by definitive proof.

Reticulo-endothelial System in Shock.

Recent research has directed attention to the role of the reticulo-endothelial system (RES) in the vascular reactions to shock. The liver, the largest single component of the RES, suffers extensive damage during protracted episodes of haemorrhagic hypotension. Broad changes in liver metabolism have been described (Engel et al., 1944), as well as specific alterations of the mechanisms concerned with the storage and release of the iron-bearing protein, ferritin (Shorr et al., 1951). Although the recent emphasis on bacterial factors has shifted attention away from the possible release of vasotoxic products by the liver *per se*, the functional integrity of this organ is unquestionably a decisive factor in determining the outcome of the shock syndrome. The release of bacterial endotoxins from the intestinal tract into the circulation cannot by itself account for the lethal course of the syndrome under different experimental conditions. When the phagocytic function of the RES is depressed by blockade, the animals are much more sensitive to the lethal effects of endotoxin (Beeson, 1947). It was conceivable, therefore, that during haemorrhagic shock reticulo-endothelial function becomes depressed as a consequence of liver hypoxia, and thereby leads to the systemic spread of endotoxins. Such a change would explain why shocked animals are so extraordinarily sensitive to endotoxins, as Fine and co-workers have reported. We therefore made measurements of the capacity of the RES in the shocked animal to clear carbon and radio-active chromium phosphate from the bloodstream (Zweifach and Benacerraf, 1958).

The clearance studies showed that phagocytic activity was reduced by several hundred per cent in rats and rabbits subjected to graded haemorrhage, transfused and eventually shown to be irreversible. Phagocytic activity was maximally impaired within 2 hours after the induction of hypotension and continued to be depressed, even in animals that survived for 48–72 hours. Another index of RES function, the efficiency of clearance, was measured by injecting isotope-labelled col-

loids in extremely small amounts, well below maximum uptake values. The findings indicated that phagocytic function was impaired following haemorrhagic shock because of an inefficient removal of these colloids (table IV).

TABLE IV

Effect of Haemorrhagic Shock on Liver Circulation and Reticulo-endothelial Function.

		Phagocytic index (K)	Efficiency (per cent) (Ke)	Liver blood flow (ml/gm/min)
Rat				
Controls	(6)	0.032	75	1.6
Shock	(6)	0.015	13	1.1
Rabbit				
Controls	(9)	0.025	84	1.5
Shock	(8)	0.017	45	1.4

Removal of albumin iodinated with I^{131} was used to measure rate (K) and efficiency of clearance. Liver blood flow was calculated from Neparian index (Ke), blood volume and efficiency. In shock experiments, the blood pressure was kept at 35 mm Hg for 2 hours and clearance recorded 1 hour after blood replacement.

The uptake of carbon by the Kupffer cells provided a means of identifying by histological inspection the vessels in the liver parenchyma through which blood was actively flowing (Zweifach and Benacerraf, 1958). In normal animals, carbon is uniformly distributed throughout the Kupffer elements of the liver lobule. Following an episode of graded haemorrhage, the uptake of carbon is confined to the Kupffer elements in the periportal areas, while the more centrally placed phagocytic cells were completely devoid of particulate material. The abnormal distribution of carbon was taken to indicate a restricted circulation which bypassed the central portion of the liver lobules. A similar restricted pattern of distribution was also observed in rats which had been subjected to traumatic shock in the Noble-Collip drum. On the other hand, in animals in which reticulo-endothelial function was depressed by the injection of bacterial endotoxins, histological inspection showed that the uptake of carbon had been uniformly reduced in all the Kupffer cells in the liver. Obviously, the haemodynamic changes, during haemorrhagic shock, are much more complex than those which can be attributed to overwhelming endotoxaemia *per se*.

In a previous section, it was indicated that the primary factor in both the predisposition and the resistance to shock may be the concomitant effect on the RES. This important system can be shown to be abnormal for at least 48–72 hours following an episode of shock. In normal animals, the RES can be stimulated by the repeated administration of colloidal substances, to the extent that phagocytic activity is increased by a factor of 3 to 5. In contrast, animals subjected to graded haemorrhage show a complete inability to be stimulated by such measures for periods up to 7–10 days after being successfully treated by blood replacement. The subnormal state of the RES is also demonstrated by the response to blockade procedures. In normal animals, blockade of the RES with carbon or saccharated iron oxide persists on the average for 8–12 hours. In contrast, blockade of the RES in animals subjected to either haemorrhagic or traumatic shock suppresses RES activity for periods of 3–5 days before this function begins to return to normal levels. The status of the RES in shocked animals after therapeutic treatment is of considerable importance, since the response of the animal to the challenge of bacterial infection, depends in large part upon the capacity of the RES to be stimulated.

Most discussions of the role of the RES in different experimental states are concerned with the phagocytic activity of these cells, usually in relation to the clearance of bacteria or their products from the bloodstream. Well-documented evidence shows that this represents only one aspect of the diverse functional activities of these cells. Several of these potential functions are relevant to our discussion of the aetiology of shock. As previously indicated, the biological inactivation of ferritin is dependent upon the reticulo-endothelial elements. During the progression of the shock syndrome, the capacity of the liver to inactivate ferritin is lost. This metabolic defect may be related to the depressed state of the RES at this time. Although a systemic function of ferritin release has not been established, the ultimate outcome of the shock reaction may depend on the extent to which factors of

this type disrupt vascular regulation within the liver proper. Another function of the RES is indicated by *in vitro* perfusion of tissues taken from animals subjected to blockade of the RES. Although the colloids used to produce blockade were taken up almost entirely by the liver and spleen, the effects of the reaction were manifest in other structures. For example, the vessels in the ear and hind limbs of blockaded animals, when perfused under *in vitro* conditions, were found to be unusually sensitive to the toxic action of even minimal doses of bacterial endotoxins. Furthermore, the endothelium of preparations from blockaded animals avidly phagocytizes colloidal materials when perfused under *in vitro* conditions, as contrasted with the inactivity of normal endothelium. These experiments demonstrate a hitherto unsuspected function of the RES in maintaining vascular tone. A complete accounting of the role of the RES in the shock syndrome must also consider the possible elaboration of materials such as properdin, which contribute to the so-called "natural resistance" of the animal. Properdin levels in the blood fall precipitously after blockade of the RES and remain low for almost 24 hours.

Protective Modalities.

The capacity to withstand shock can be increased by repeated exposure to sublethal doses of trauma. Thus, in the case of shock induced by rotating animals in the Noble-Collip drum, it is possible to develop a high degree of resistance to injury that is severe enough to be 100 per cent lethal to controls (Noble, 1943). Although the precise mechanism for this type of resistance is unknown, it was recognized that animals would lose this capacity when they become infected. One of the many features of infection is that it inhibits the activity of the RES. We therefore tried to overcome resistance by overloading the RES with particulate materials to the point where phagocytic function was significantly lowered. Trauma-resistant rats, pretreated with carbon, no longer show an enhanced capacity to withstand shock.

These considerations led us to examine the adaptive process leading to resistance, centering our attention on the contribution of the RES. In view of the suggested role of bacterial endotoxins in the induction of lethal shock, we first considered the possibility that the adaptation to drum trauma was based on an increased resistance to bacterial toxins. This proposition was tested in two ways—by administering lethal doses of bacterial endotoxins to drum-resistant rats, and by inducing tolerance to bacterial extracts through repeated exposure to these substances.

The experiments with lethal amounts of endotoxins were inconclusive, since only a small proportion of trauma-resistant rats (20–30 per cent) show an increased tolerance to bacterial extracts. Much more information was derived from studies of the response to haemorrhagic and traumatic shock in animals with induced tolerance to endotoxins.

Endotoxin Tolerance.

Tolerance to a particular extract of gram-negative bacteria does not depend upon an antigen-antibody response, and is sufficiently broad to be effective against extracts of many other gram-negative forms. The tolerance can be sustained for extended periods by periodic challenges with endotoxin. Rats and rabbits were made tolerant by injecting graded amounts of endotoxin (*E. coli*) on five successive days. Standard shock, either haemorrhage or drum trauma, was induced from 48 to 72 hours later. The findings unequivocally demonstrate a high degree of protection against lethal doses of trauma or haemorrhage (Zweifach et al., 1957).

Stimulation of RES.

At first glance these experiments would seem to prove conclusively that endotoxins are directly involved in the evolution of the irreversible state. Other considerations, however, cannot be construed in this light. The induction of tolerance to bacterial endotoxins is consistently associated with a stimulation of the RES, as manifest by an enhanced capacity to clear collodial material from the bloodstream. Inasmuch as the RES can be stimulated by repeated administration of chemically inert colloidal materials, we were interested in finding out whether animals, whose RES had been stimulated by unrelated means, were then tolerant of haemorrhagic and traumatic shock. This was actually found to be the case. Stimulation of the RES by nontoxic colloids was found

to be equally effective in making rats resistant to normally lethal shock (Zweifach et al., 1957).

Differences do exist between endotoxin-tolerant animals and those in which the RES had been stimulated by nonspecific colloids (table V). Animals with an increased phagocytic capacity

TABLE V
Protective Modalities in Shock

Pretreatment	Clearance by RES	Cross tolerance: Endotoxin	Cross tolerance: Haemorrhagic shock
Endotoxin tolerance	Stimulated	++	++
Denatured albumin	Stimulated	0	++
Zymosan	Stimulated	±	++
Cold (0°C)	Mod. stim.	0	+
Drum resistance	No change	±	++
Endotoxin tolerance and drum resistance	Stimulated	++	++
Depletion with 48/80	No change	++	+

Data based on experiments in the rat. See text for details of pretreatment measures. RES function measured by clearance of carbon from blood. Animals challenged with 3.0 mg *E. coli* endotoxin, and haemorrhagic hypotension. Blood pressure kept at 35 mm Hg for 3 hours.

were not uniformly tolerant to bacterial endotoxins. In fact, stimulation by other polysaccharides, such as the yeast extract zymosan, did not confer any appreciable tolerance to endotoxins, although the tolerant animals were resistant to drum shock and haemorrhage, and to challenge with whole bacteria. Our observations that drum-resistant rats did not show a stimulated RES phagocytic capacity (Zweifach et al., 1957) would indicate that tolerance involves broad changes common to several forms of adaptation, but in each instance the tolerant state has specific attributes which are not necessarily found in the others.

Relative Importance of Liver and Bowel.

The renewed interest in bacterial elements served to shift the emphasis to the intestinal tract, where this toxic factor originates. Extensive pathology involving intramural and intraluminal haemorrhage within the gut is consistently observed during shock. This circumstance raises the question whether the gut is important not only as a source of systemic contamination, but as the major site for vascular decompensation and extravascular sequestration of blood. Perfusion experiments have provided some answers to these questions. In their earlier studies dealing with cross transfusion Frank et al. (1946) reported that viviperfusion of the liver protected dogs against the irreversible aspects of the haemorrhagic shock syndrome. They were unable by surgical removal of the gastro-intestinal tract to demonstrate any protective action. More recently, Lillehei (1958) and Kessler et al. (1958) found, when the intestinal tract was perfused by way of the superior mesenteric artery, that the number of survivors following graded haemorrhage was greatly increased (70 per cent as compared with 10 per cent). Perfusion of other organs, including the liver, was not as effective.

Obviously, we are dealing in the case of the liver and bowel with interlocking vascular systems, which make it difficult to delineate cause and effect. In the intestine, two modes of involvement are indicated. The bacterial flora in the lumen of the intestine can give rise to toxic products, in the form of bacterial invasion *per se*, endotoxin derivatives, or split products resulting from bacterial action on foodstuffs. In each of these instances, the substances exert a local effect directly on the bowel wall, and a systemic effect as a consequence of their dissemination by the circulation and the lymphatic system. Under normal circumstances, foreign materials entering the bloodstream from the bowel are removed by the Kupffer elements of the liver. Materials taken up by the lymphatics usually pass through regional lymph nodes which serve a comparable detoxifying function. Protracted shock impairs reticulo-endothelial function to the extent that the Kupffer elements no longer effectively remove bacteria or their products from the portal circulation. Whether the reticulo-endothelial elements of the regional lymph nodes develop a similar defect under conditions of shock is not known. We have only fragmentary information concerning the status of this potential pathway of toxicity.

Not all forms of tolerance or resistance to shock are associated with a heightened or stimulated phagocytic function of the RES (table V). However, unlike controls where the functional activity of the RES is depressed by noxious stimuli (haemorrhage, trauma, endotoxins), the cells of tolerant animals maintain their phagocytic

efficiency following severe shock, irrespective of the method used to induce tolerance. Protection is also correlated with an almost complete absence of pathology in the bowel, despite the presence of bacterial elements in the intestinal lumen. Apparently, separate protective modalities can be stimulated in the bowel or liver independently of one another.

The fact that blockade of the RES not only predisposes to shock, but also circumvents resistance to all types, including that engendered by autonomic blocking drugs and antibiotics, strongly suggests a major function for this system. The opposite facet of the problem, namely increased tolerance, cannot be explained on the basis of changes in the formation and detoxification of toxic factors in the bowel or liver.

Protective Action of Amine Depletion.

Recent work has focused attention on another of the wide variety of biological processes concerned with the adaptation to different noxious stimuli. The phenomenon of drum resistance involves an interesting facet which has not been given sufficient consideration. The trauma inflicted by the rotating drum method, in the case of normal rats, produces diffuse haematoma at all of the body prominences in the skin. On the other hand, drum adapted or resistant rats, even when exposed to severe trauma in the drum, show almost no evidence of vascular petechiae or haematoma. This unusual circumstance brought to mind the observation made by Rowley and Benditt (1956) that the administration of agents of the histamine release class, which deplete the skin of vaso-active amines, protect the skin vessels against different forms of injury. It seemed reasonable to assume that repeated episodes of stress during the adaptive regime, resulted each time in the release of tissue mediators, and thereby modified the subsequent response to trauma.

We tested the validity of this thesis by treating animals with a number of so-called histamine releasers (Zweifach, 1958). One of the agents, commonly used to liberate tissue amines, is compound 48/80. When a rat is injected with a single large dose of 48/80, the animal invariably dies. It is possible by giving 4 to 5 doses at daily intervals, to make the animal completely refractory to the hypotensive and amine-releasing action of this drug. Previous workers attributed this phenomenon to the depletion of tissue amines such as histamine, 5-hydroxytryptamine and noradrenaline.

Animals treated for several days with 48/80, became resistant to both haemorrhagic and traumatic shock (table VII). These animals were also tolerant of normally lethal doses of gram-negative bacterial extracts. We therefore advanced the working hypothesis that different adaptive procedures have, in common, some effect on the local tissue mediators. Unlike other forms of resistance, 48/80 tolerance did not stimulate the phagocytic behaviour of the RES (see table V).

The simplest explanation of the above experiments would be to assume that the protective modality depletes tissue mediators normally involved in vascular injury. It is equally plausible that the repeated release of tissue amines leads to adaptive mechanisms which permit the tissue to handle substances of this type more efficiently. Compound 48/80, as well as other histamine releasers, are reported (Rowley and Benditt, 1956) to mix with various blood constituents and to alter the blood clotting system. Here again, as

TABLE VI

Effect of Amine Depletion with 48/40 on Lethal Shock in Rats

		Survival statistics	
	Drum trauma	Haemorrhage	Endotoxin
Controls	3/20 (15%)	3/12 (25%)	4/30 (13%)
48/80 treated (5 days)	16/20 (80%)	8/12 (67%)	25/30 (83%)

Drum trauma=750 turns in Noble-Collip drum.
Haemorrhage=Blood pressure at 35 mm Hg for 3 hours.
Endotoxin=Extract of *E. coli*, 3.0 mg (i.p.).
Fraction in survival columns indjcates number of survivors in numerator and total number of animals in denominator.

TABLE VII

Response of Microcirculation in Rats treated with Amine Depleter, 48/80.

	Dose	Vessels in skin	
		Controls	48/80 treated
Adrenaline	1 μg—local	General constriction.	Slight constriction.
5-Hydroxytryptamine	0.5 μg—local	Adrenaline reaction inhibited.	No change.
Acetylcholine	1 μg—local	Dilatation of arterioles-precapillaries.	Dilatation only of precapillaries.
Histamine	5 μg—local	General dilatation.	General dilatation.
Drum trauma	750 turns	Petechiae.	None.
Endotoxin (*E. coli*)	500 μg—i.p.	Venospasm.	None.

in the case of experiments with the RES, the evidence indicates that animals can be made tolerant to stress by activating different homoeostatic systems, although no single one is essential for the process. It is probable that the syndrome develops differently under particular circumstances and in different species. The relative importance of any factor must be weighed separately in each specified instance.

Evidence against Bacterial Factor in Shock.

A considerable number of experimental studies do not conform with the bacterial concept of shock. The following represent areas of our own work which we have not been able to reconcile with such an hypothesis. In a previous section, we cited the contradictory experiments with germ-free animals. Other reservations arose when we attempted to corroborate the bacterial concept by modifying experimental conditions so as to predispose or enhance the reaction to protracted shock.

If the bacterial thesis is correct, a correlation should exist between the susceptibility of an animal to endotoxin, on the one hand, and its resistance to shock, on the other. One of the interesting experimental models available for clarification of shock mechanisms, is the delayed type of hypersensitivity that can be induced in guineapigs by pretreatment with tuberculin extracts (Stetson, 1955). These animals, in addition to their specific sensitivity to challenge with tuberculin, are also unusually susceptible to the systemic effects of bacterial endotoxins. Sensitized guineapigs are up to 10 times more responsive to extracts of gram-negative bacteria than normal guineapigs. We therefore attempted to test the specific contribution of bacterial endotoxins to the evolution of the shock syndrome in such animals. Full sensitivity was allowed to develop (4 weeks) before inducing haemorrhagic shock. The experiments failed to demonstrate any clear-cut differences between control and sensitized guineapigs in their response to shock. Many of the sensitized guineapigs were actually more resistant to protracted graded haemorrhage. Aside from the obvious conclusion that bacterial endotoxins do not contribute significantly in the guineapig to the irreversible phase of haemorrhagic shock, the experiments confirm the existence of species differences in this regard. Caution must be exercised before extending the importance of bacterial factors to shock as a general entity.

Although the development of resistance is associated in many instances with stimulation of the phagocytic behaviour of the RES, further investigation of these variables does not support a direct relationship between tolerance to bacterial endotoxins and stimulation of the RES.

Zymosan, a yeast extract, when given repeatedly, serves as an unusually effective means for stimulating the RES, as manifest by measurements of phagocytic clearance. Experiments were conducted to ascertain to what extent this type of RES stimulation was associated with a resistance to different lethal agencies. Although zymosan-treated rats were clearly resistant to both traumatic and haemorrhagic shock, they were not tolerant of normally lethal doses of bacterial endotoxins. As in the case of drum resistance, we encounter here a dichotomy between the susceptibility to shock and to bacterial endotoxins. We must conclude that

stimulation of the RES, as measured by its phagocytic activity, does not *per se* adequately reflect the nature of the changes induced by various forms of adaptation. In addition to a broad change in phagocytic activity, the capacity of the reticulo-endothelial cells to metabolize particular substances undergoes adaptive changes which are highly specific in terms of the stimulating agent.

Antibiotics are believed to protect against the lethal effects of shock by suppressing the bacterial flora in the gastro-intestinal tract, and thereby reducing the invasion of bacterial products into the systemic circulation. This explanation cannot be readily reconciled with the fact that antibiotic-protected animals lose their resistance to shock when the RES is blockaded with carbon or thorotrast. In normal animals, blockade of the RES increases the sensitivity to bacterial endotoxin, a feature which presumably accounts for the increased susceptibility to shock at this time. Precisely why blockade should circumvent the protective effect of antibiotics is difficult to establish on the basis of the above considerations alone. Metabolic and pharmacological properties, other than the antibacterial potential, must also be considered.

Fine and co-workers previously reported that animals receiving either a single or split dose of endotoxin were protected against a subsequent lethal injection of endotoxin if an antibiotic was given together with the original endotoxin (Schweinburg et al., 1956). The split dose regime is much more toxic than a single dose procedure. Thus, in rabbits, 25 gamma of an *E. coli* endotoxin, when followed by a second dose of as little as 5 gamma within 1 to 2 hours, is uniformly lethal. Bacitracin, penicillin, or polymyxin, given with the first dose of endotoxin, rendered the second dose ineffective. Inasmuch as endotoxaemia is uniformly associated with an impaired phagocytic function, we carried out experiments to determine whether antibiotics under these conditions overcame the toxic depression of the RES.

A single dose of antibiotic completely abrogated the usual depressant action of the endotoxin on the RES. The conventional antibacterial effects of the antibiotic apparently were not involved, in view of the short duration of the experiment (30–120 minutes). It is pertinent in this regard to note that administration of autonomic blocking drugs, coincident with the initial dose of endotoxin, likewise served to negate the depressant effect of bacterial products on the RES. These experiments suggest that interference with the phagocytic activity of the RES following endotoxaemia may depend upon a chemical mediator, possibly adrenaline or 5-hydroxytryptamine, both of which are blocked by drugs such as chlorpromazine or dibenzyline, the most effective agents in this regard.

General Conclusions.

The various concepts that seek to explain the development of the shock syndrome, cannot be readily brought into a single unifying hypothesis. Two organ systems are clearly involved in the decompensatory trend leading to irreversibility —the intestinal tract and the liver. The hepato-renal hypothesis, by its very nature, emphasizes the importance of functional changes in the liver. Protracted shock leads to disturbances of liver metabolism, manifest by extensive changes in blood chemistry, elevated uric acid levels, an increase in blood iron, and, in support of the primary thesis of the hepato-renal concept, the liberation of the iron-bearing protein, ferritin. Viviperfusion of the liver protects the animal against shock. When the liver circulation was arterialized by anastomosing the portal vein with the renal artery (Baez et al., 1953), the irreversible aspects of severe haemorrhagic shock were avoided. The fact that blockade of the Kupffer elements of the liver abrogates all forms of tolerance, further confirms the importance of this organ system to the overall response to shock.

The intestinal tract has an equally important role in the shock reaction. Our analysis of the "gut factor" indicates at least four separate elements: (1) bacteria are present in the lumen of the bowel and can give rise to toxic products; (2) the intestinal wall sets up a local defence barrier, which normally does not permit bacteria or their products to enter the circulation; (3) the systemic distribution of these toxic agents occurs by way of the blood and lymphatic system; (4) local tissue damage results from the combined effect of stagnant hypoxia and a superimposed endotoxaemia.

In animals such as the dog and rabbit, the major component of the "gut factor" would appear to be bacterial contamination. It has been assumed that antibiotics protect the shocked animal by destroying the bacterial flora responsible for the toxic element. The presence of bacteria in the bowel may also give rise to toxic amines, as a result of bacterial action on foodstuffs, rather than to direct infectious action *per se*. We have provided evidence that antibiotics protect the reticulo-endothelial system against the depressant action of bacterial products. When the RES is stimulated by inducing tolerance to endotoxins or by repeated injection of colloidal agents, the lethal effects of severe shock are abrogated, presumably because circulating toxins are handled more effectively. During the process of adaptation of the RES, the peripheral blood vessels in general are affected as well, and show an increased resistance to tissue injury. The suggestion was made that a vascular hormone regulated by the RES may exist. The fact that perfusion of the gut is also a lifesaving feature can be explained in several ways. The conventional interpretation is that the improved blood flow suppresses the elaboration and release of endotoxins from the bowel. It is also conceivable, when the integrity of the gut is maintained through perfusion measures, that the liver circulation is not affected by the stagnant hypoxia to the same extent as in normal shock situations.

Autonomic blocking drugs prevent the congestion and haemorrhage of the gut regularly present in control animals following shock. These pharmacologic agents are presumed to act in two ways: by modifying the extreme vasoconstriction during the compensatory phase of the syndrome, and by blocking the vasotoxic effects of bacterial products or endotoxins. It is significant that the wall of the gut in animals treated with dibenzyline or chlorpromazine, shows little or no vascular damage despite an attendant bacteraemia (Zweifach and Hershey, 1957). It might be argued that local pathology in the gut wall is an essential part of the dissemination of bacterial toxins, since the wall normally serves as an effective barrier. On the other hand, fatal shock can be avoided despite the presence of extensive gut damage and bacterial toxaemia, when the integrity of the RES is maintained, as in the case of experimental stimulation of the RES.

A shift in emphasis to bacterial factors does not by itself appreciably clarify the mechanism of vascular collapse. In the case of bacterial endotoxins, we have substantial evidence that their vasotoxic effect is related to adrenaline (Zweifach et al., 1956). Many adrenergic blocking drugs do not, however, afford effective protection.

Both the adaptation to drum trauma and the depletion of amines from the tissues of animals treated with histamine releasers seem to protect by suppressing the massive release of vaso-active amines, usually associated with severe shock. It is highly probable that the release of these amines is an essential step in the vasotoxicity associated with many forms of tissue damage.

We face a puzzling situation in regard to the counter-effect of RES blockade on the resistance imparted by 48/80 depletion measures. If these amines are indeed the final mediators of the vasotoxic sequelae of shock, how can this effect be disrupted by blockage of the reticulo-endothelial elements in the liver and spleen? Possibly, this could be accounted for by the endocrine function postulated for the reticulo-endothelial elements on the basis of *in vitro* studies of peripheral blood vessels.

The experiments with germ-free animals, likewise, require careful interpretation. Germ-free rats regularly develop irreversible shock despite the complete absence of bacterial contaminants and obvious sources of endotoxins. Recent studies (Benacerraf et al., 1958) on the RES of germ-free mice and rats indicate that both the phagocytic function and the capacity to be stimulated are well within the range of normal laboratory animals. The only explanation, which might be reconciled with the implications of the bacterial concept, would be that offered by Landy and Shear (1957). Their work has led them to believe that tissues in general contain polysaccharide components, which when liberated reproduce the pathological effects of bacterial endotoxins. They have suggested that the toxic factor in the germ-free rat may be due to the elaboration of an endogenous toxin of this type.

The relation of the ferritin defect to other homeostatic systems has not been thoroughly established. A close chronological parallelism

exists between the overflow of ferritin into the circulation and vascular decompensation in the viscera. The release of ferritin from the liver parenchyma occurs at the very time when the RES shows signs of impairment. Recent studies, in which the reticulo-endothelial cells of the liver were separated from parenchymal cells under *in vitro* conditions, indicate that the inactivation of ferritin occurs only in the presence of Kupffer cells. The bacterial factor may be related to the ferritin system in two ways—by depressing the activity of the RES, and by a common influence on the vascular response to catechol amines.

One other circumstance, regularly encountered in shock, has some bearing on the general topic under discussion. Different forms of tissue damage, including protracted haemorrhagic shock, are known to lead to an increased proteolytic activity of the blood (Zamecnik et al., 1945). Increased proteolysis exaggerates the endotoxin reaction and by itself leads to various forms of vascular damage (Schneider, 1950). We have preliminary evidence that animals, primed with various adaptive regimes, maintain their blood proteolytic activity at normal levels and thereby may be protected against many of the lethal manifestations of shock. Blockade of the RES is, by itself, associated with an increase in the proteolytic activity of the blood. Also, the injection of bacterial endotoxin enormously increases blood proteolytic activity (McKay and Shapiro, 1958). The relation of these changes to local vascular homeostasis requires further study.

No single description of the shock syndrome can possibly reflect the seemingly endless series of overlapping homeostatic mechanisms, on a local and systemic level, which contribute to the ultimate pathology during different forms of shock. Although the basic elements in the shock process have been defined, we must still establish the relative importance of the physiological processes which integrate these homeostatic systems.

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HOST RESISTANCE TO BACTERIAL INFECTION IN TRAUMATIC SHOCK*

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IT may be tiresome to labour the point that the cure of bacterial infections is seldom if ever achieved by antibiotics alone, and that their complete elimination requires of the host an intact antibacterial defence system. We are familiar with some of the components of this system, e.g. the granulocyte and the macrophage, and plasma factors such as complement. We also are aware of the role of the kidney and the biliary tract as routes for the excretion of bacteria, of the cilia in the tracheobronchial tree combined with the cough mechanism for the expectoration of lung secretions, of the cilia in the nasal sinuses, of the antibacterial capacity of the lacrimal secretion, and of the hydrochloric acid in the stomach. We know of the filtering function of the lymph nodes, and of the white cell layer distributed throughout the submucosa of the nasopharynx and of the small and large intestine. These are all vital functions serving the local and general defence, and their mode of operation is for the most part plain enough. Other subtler ones work biochemically and enzymatically. Of the latter mechanisms we probably know only a small fraction of the total number, and, apart from specific immunological phenomena, almost nothing of their nature. More recently, some of them have begun to yield to the probings of the basic scientist and the research clinician. Thus, a lysozome in granulocytes has been isolated. Tullis (1956) has recently identified two phagocytosis-promoting factors in plasma; Hirsch (1956) has isolated from granulocytes a bactericidal enzyme, "phagocytin", which destroys a restricted number of bacterial species; and Myrvik and Weiser (1955) have identified a plasma component which is bactericidal for B. subtilis. Landy et al. (1957) identified an endotoxin-detoxifying component in serum that may or may not be the alkaline phosphatase which, according to Rowley (1956), inactivates the lipopolysaccharide of endotoxins by splitting off phosphate. Wood and Smith (1946) have beautifully elucidated some of the mechanisms governing the ingestion of bacteria by phagocytes, and have depicted the process of transcapillary migration of granulocytes in response to an extravascular irritant. Miles and Wilhelm (1955) have demonstrated two factors in the plasma of guinea-pigs, one of which facilitates, while the other inhibits, the egress of fluids from the capillaries to a site of challenge.

Also noteworthy is the discovery by Pillemer (1954) of properdin, a globulin in plasma which, in the presence of a critical concentration of Mg ion, activates the C^3 component of complement to lyse extracellular bacteria. This, he finds, is due to its affinity for certain polysaccharides of high molecular weight in the bacterial cell walls, chiefly of the gram negative flora, such as B. Proteus and Aerobacter Aerogenes, which are so frequently resistant to antibiotic therapy. Properdin is present in the serum of all mammals so far studied, but with wide variations in titre in different species: in the mouse and rat the titre varies from 25 to 50 units/ml, in the guineapig it is about 2 units/ml, and in man 4–8 units/ml. What this signifies with reference to species differences in natural resistance to infection remains to be shown.

There are as yet no data on the effect of the depletion of properdin upon survival from infection due to properdin-sensitive bacteria, except the intriguing observation by Pillemer that post-radiation bacteremia in rats occurs at about the time (fifth to seventh day) when properdin has disappeared from the blood; and that the administration of properdin at this time eliminates the bacteremia, and prevents death from infection. X-radiation is only one of the agents which deplete properdin. Malnutrition is another. Thus stray dogs, which constitute the ordinary laboratory's dog farm population, frequently have a low

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properdin titre, or develop one if not properly cared for. There are geographical factors involved also. Thus 60 per cent of the dogs brought to our animal farm in Boston have a normal titre (12–18 units/ml), and over 85 per cent of the beagles in the A.E.C. animal farm in Rochester, N.Y., which are especially well cared for, have a better than normal titre (up to 25 units/ml). On the other hand most of the stray dogs in Cleveland, Cincinnati and Houston tested by Pillemer showed a low to undetectable titre. Good care and good food can restore a low properdin titre to normal (Pillemer, 1954).

Whether the capacity of dogs to tolerate various types of trauma is related to the properdin titre is not known. We have observed that haemorrhagic shock in dogs promptly depletes the serum of its properdin (Frank et al., 1955). The same is true of tourniquet and drum shock in rats (Pillemer, 1955). To adequately assess the importance of this substance in the overall defence against infection will require a considerable supply of the purified material for clinical and experimental study. Its isolation from human and animal blood is difficult, and has not yet been achieved in sufficient quantity for proper exploitation. Hopefully, the Protein Foundation in Boston, which is now engaged in this effort, will produce enough to allow procurement of some preliminary data. Meanwhile, it is worth noting what Dubos and Pillemer have repeatedly emphasized: that properdin is almost certainly only one of a whole galaxy of natural protective substances that remain to be discovered.

The beautifully precise experiments of Dubos (1954) on the effect of general and specific dietary deficiencies on the natural defence against infection emphasize what is empirically known to the clinician: that malignant disease, diabetes, ulcerative colitis and other constitutionally depleting disorders can gravely weaken the defence against bacteria. Defective nutrition, and localized deficiencies, such as obstruction to flow of fluids or poor blood supply, tell us only in general terms why the systemic or local resistance has failed. What is needed for a more complete and precise understanding is more light on the biochemical systems involved in general and local tissue resistance, especially when overt tissue injury is not apparent.

For the exploration of this problem traumatic shock is a convenient experimental tool, because the rapid deterioration resulting from acute tissue anoxia involves the antibacterial defence mechanisms as well as many other vital processes. The remainder of this essay is concerned with an analysis of the structural weaknesses in the host's resistance to infection in traumatic shock. As this study was an outgrowth of an attempt to solve the problem of the refractory state of traumatic shock, it may be of some interest to present the data more or less in the chronological order in which they were obtained.

Until 1940 the controversy over the frequent failure of animals with traumatic shock to respond to blood volume replacement therapy centred in theories on the fate of the transfused blood. In the next few years, after blood volume measuring techniques became sufficiently reliable, it was found that the transfused blood remained for the most part in the circulation, and the concept of excessive capillary permeability was shown to be an untenable hypothesis. Chambers and his collaborators (1944), with the use of in-vivo microscopy of the peripheral circulation, made a big step forward by showing that most if not all the capillaries were either collapsed and empty, or congested with stagnant or at best a slowly moving column of blood. The picture uncovered was one of many dry river beds intermingled with swamps, with more of one than the other depending on the degree and duration of shock. When it was observed that even with a full complement of blood, given too late, stagnation was still present, it became evident that the fundamental difficulty was paralysis of the peripheral vascular mechanisms. Since the capillary is a passive tube from the point of view merely of the propulsion of the blood, the defect was shown to lie principally in the failure of function of the muscle layer of the venules, arterioles, meta-arterioles, and, especially, of the precapillary sphincters. In the case of prolonged hypovolaemia, as in simple haemorrhagic shock, this functional paralysis could be explained simply as one manifestation of generalized tissue injury due to persisting hypoxia. But this is a dubious explanation, because more severe and more prolonged hypoxia can be tolerated by the vessels without such paralysis—witness the satisfactory resumption of flow following release

of a total occlusion of the arterial supply to an extremity for at least as long as it takes for experimental haemorrhagic shock to become refractory to transfusion.

Thus it becomes necessary to invoke some additional factor, i.e. some kind of toxic injury to the vessels, as is doubtless the case in normovolaemic septic shock. The theory that a toxin is responsible for death when hypovolaemic shock fails to yield to apparently adequate therapy is an old one, which has been investigated time and again. In simple haemorrhagic shock that has become refractory to transfusion the usual evidence for infection as a possible source of toxin is not present. Might infection be present nevertheless?

Before further discussion of the evidence for bacterial toxins, we may refer to the evidence for toxins of nonbacterial origin. Exogenous toxins of nonbacterial origin have been found capable of producing shock; but little illumination on the aetiology of the refractory state of traumatic shock can be looked for from such studies. Endogenous toxins, such as released myoglobin, haematin, callicrein, various tissue degradation products, and tissue metabolites have been studied intensively, but with insufficient evidence that they play a crucial role.* However, Landy and Shear (1957) have isolated polysaccharides with endotoxin-like properties from the tissues of normal plants and mammals. Since these properties are not elicited by tissue extracts until after treatment with trypsin, there is serious doubt that the catabolic processes in shock could produce substances requiring the violence of trypsinization to impose an endotoxin-like behaviour upon them. We should here refer in some detail to the work of the late Dr. Ephraim Shorr and his collaborators (1951) on an iced saline extract of liver from the shocked animal, which they named VDM (vasodepressor material), and which they eventually identified as reduced ferritin, i.e. ferritin in which an S-S linkage is reduced to an S-H linkage because of the low oxygen supply to the liver. Circulating VDM was said to be responsible for irreversibility to transfusion because, when given intravenously to the rat, it increased the amount of topically-applied adrenaline required to evoke a vasoconstrictor response in the appendiceal mesentery. Most investigators in the field regard this as insufficient evidence, on the ground that the same effect is not observed in other fields of the peripheral circulation. My colleagues and I could not obtain a fall in blood pressure with intravenous doses up to 1,000 times the dose stated to be depressor, when given to dogs whose kidneys and liver had been removed to prevent its excretion or inactivation (Frank et al., 1952).

When the kidneys, the adrenals, the lungs, the heart and central nervous system were excluded for various reasons as vital organs whose failure to function might explain the refractory state of the peripheral vessels, we centred our attention upon the liver about the same time as Shorr and his collaborators, and observed that perfusion of the portal vein of the dog in haemorrhagic shock, by cross-circulation with arterial blood from a donor dog, prevented the development of irreversibility to transfusion (Frank et al., 1946). (Perfusion of a systemic vein did not protect the recipient.) We stated then that the perfusion served either to protect some liver function essential to the integrity of the peripheral circulation, or to prevent the elaboration of some toxic substance. In further pursuit of the explanation of the effect of cross-circulation we speculated that maintenance of adequate tissue nutrition of the liver should preserve its antibacterial potential, among other functions. Since collapse of this function might allow bacterial toxins from invading intestinal flora to be released, and so injure the peripheral circulation, just as overt septic shock appears to do, we proceeded to investigate the antibacterial mechanisms directly. In the ensuing years we obtained considerable evidence in support of the thesis that collapse of this function did occur, and that bacterial activity, i.e. bacterial toxins, were indeed involved in the development of the refractory state, in spite of the absence of the usual signs of infection.

The evidence was as follows: The first observation was that the course of a standardized type of haemorrhagic shock, described elsewhere (Fine, 1954), is the same whether

* Electrolyte imbalance, including acidosis, which may lead to the production of abnormal metabolites has been thoroughly studied, and should be discarded as a likely factor, for it has been shown that whereas such imbalances can cause shock, the course of shock can be relentless in many instances when there is no electrolyte imbalance, or after the imbalance has been fully corrected.

the experiment is performed with or without aseptic technique. Therefore, if bacteria were operating, they were not bacteria that we might be introducing during the experiment. The next observation dealt with the bacteriology of the dog's tissues. Clostridia are present in the tissues of various mammals, especially the dog, in which they are found in greatest frequency and numbers in the liver. Aub and his collaborators had previously shown that the transudate from ischaemic muscles of the dog contain Clostridial toxins, which can be lethal when given intravenously to other dogs (Aub, 1944). Since the Clostridia in the muscles as well as in the liver might be a major source of toxins in a shocked animal, we tried to prevent the development of irreversibility to transfusion by the use of polyvalent Cl. antitoxin, and by the prophylactic use of Cl. toxoids, but to no avail. We also tried penicillin and aureomycin intravenously during shock. These drugs doubled the survival rate, i.e. from a maximum of 20 per cent in a large series of dogs to 40 per cent in some 20 experiments. This was not impressive enough to demonstrate a decisive role for a bacterial factor. Later, in the course of other work requiring the oral administration of antibiotics, we repeated these experiments, giving aureomycin orally and in large doses for several days in advance of producing the shock. To our amazement 20 of the first 25 dogs so treated recovered completely (Frank et al., 1952). Particularly striking was the treated dog's ability to tolerate a continuously sustained systolic blood pressure level of 30 mm Hg for a much longer time than the untreated dog. In the untreated dog in haemorrhagic shock this level of blood pressure is not tolerated for more than an average of 5 hours, and restoration of normovolaemia at that time produces only a transient pressor response, with death following some hours later. On the other hand, when the treated dog was transfused after 6, 7 or 8 hours, the blood pressure response was excellent and well sustained, and the dog was frequently able to stand and drink water within an hour or two.

With these preliminary observations—i.e. that intravenous antibiotic therapy *during shock* was of slight value, whereas oral antibiotic therapy given *prior* to the induction of shock was of very considerable value—we proceeded to an intensive study of the role of timing and the route of administration. The oral route was found to be not significantly better than the intravenous route, but prophylactic therapy was decidedly superior to therapy during shock. Moreover, if the aureomycin was given 3 hours before inducing shock, the result was distinctly better than when given just prior to the haemorrhage. (The effect of timing will be discussed further.)

Because the oral dose originally employed was relatively large, a non-antibiotic property of this drug was considered as a possible mode of action. This view was eventually dismissed on the following evidence: (*a*) a good effect could be obtained with an intravenous dose within the normal therapeutic range; (*b*) other antibiotics such as neomycin, terramycin and penicillin were also effective. The fact that streptomycin and chloramphenicol were considerably inferior to these was puzzling, but might be explained on the basis of insensitivity of the bacteria involved. In any case, the decidedly favourable effect of three chemically unrelated drugs, two of which, apart from their antibiotic activity, are, if anything, toxic to tissues, could not lend weight to the view that some non-antibiotic protective action is involved.

The evidence from some 300 such experiments (Jacob et al., 1954) gave strong support to the conclusion that the development of irreversibility to transfusion in haemorrhagic shock hinged upon bacterial activity. In the subsequent search for the bacteria, the first approach was to obtain blood culture data during shock. The data from some 200 cultures of blood taken at different times and in various ways from shocked dogs did not disclose the presence of bacteria at any time until death. And, except for Clostridia, no bacteria were grown from biopsies of the liver. But some 25 per cent of all blood and tissue specimens taken *immediately* after death were positive, and the bacteria recovered were the typical intestinal flora: e.g. E. Coli, B. Proteus, Aerobacter, Aerogenes, etc. Noteworthy in this connection was the higher incidence of positive cultures from portal than from systemic blood. One might dismiss these flora as "agonal invaders", or consider them as continuously invading from the intestine during life, but elusive to disclosure because conventional bacteriologic techniques do not detect their pres-

ence when the inoculum contains less than 100 to 1,000 organisms. More recently MacDonald (1958) has been able to isolate normal intestinal flora from the mesenteric nodes of half the normal rabbits examined.

Because of the limitations of conventional bacteriologic techniques, we sought evidence for bacterial activity by the use of larger inocula and living tissue (the peritoneal cavity of the dog), as the culture medium (Schweinburg et al., 1954). The experiments were performed as follows. Sterile technique was used throughout. Normal dogs, and dogs dying of haemorrhagic shock after an ineffective transfusion, were killed and their livers removed immediately, Two hundred grams of each liver was blenderized and 150 ml of the suspension injected into the peritoneal cavity of a normal dog. Seventy per cent of these dogs survived the injection of normal liver mash or of shock liver mash. The experiment was repeated, using as recipients of the mash, instead of normal dogs, dogs which were exposed to haemorrhagic shock of 2 hours duration and then transfused. Nearly all dogs transfused after 2 hours of haemorrhagic shock recover. But they are far more vulnerable to bacteria than normal dogs, as will appear from data that will be presented later. All such dogs, injected with normal liver mash survived, but all injected with shock liver mash died. The shock liver mash, therefore, contained a lethal factor not present in normal liver mash. That this factor is of bacterial origin was shown by the observation that death of the recipient was prevented in most instances in which penicillin was given in advance. Since penicillin does not inactivate toxin, the lethal factor must have been living bacteria, either the Clostridia in the shocked liver mash which had become more virulent as a result of shock, or other species. That the Clostridia were not involved is suggested by the impotence of polyvalent Cl. antitoxins, but more significantly by the fact that neomycin, which does not act upon Clostridia was as effective as the other antibiotics in preventing irreversibility when given prior to shock.

But the main point of the experiment concerns the donor dog, which was in irreversible shock when the liver was removed. Since the bacterial activity in 200 grams of the donor's liver killed a two-hour-shock dog, then the whole liver of the donor must have been more than sufficient to kill the donor, especially one exposed to shock for much longer than the recipient of the donor's liver mash. When it was shown further that a mash of the shocked donor's muscle was also lethal for the recipient,* it was clear that the products of bacterial activity are disseminated throughout the body of the dog in haemorrhagic shock.

From clinical and experimental experience it is agreed that the duration of shock is an all-important factor in the outcome. One good reason for this can be the progressive decline in the antibacterial potential as shock continues, the evidence for which is the following:

(1) When normal dogs, two-hour-shock dogs, and dogs allowed to become irreversible to transfusion are exposed to an intravenous dose (5–50 billion) of the same bacteria, they differ in their ability to clear the blood stream (Schweinburg et al., 1954). In the normal dog less than 10 bacteria per ml remain after 6 hours. Blood cultures taken the next day are sterile, and all dogs survive. Two-hour-shock dogs clear the blood about as rapidly. But the blood cultures taken the next day are positive, and all the dogs are dead within 1–4 days, although, as previously stated, without this challenge nearly all survive indefinitely. On the other hand, about half the dogs which are allowed to remain in shock for longer than 2 hours are unable to clear the blood stream, and rapid bacterial multiplication is proceeding before they die at or about the sixth hour. Thus the defence potential grows weaker the longer the shock continues. It is of particular significance that if these bacteria are injected into a two-hour-shock dog *after transfusion, or at any time up to 24 hours later*, the dog also succumbs in bacteraemia. It is not until more than 48 hours after transfusion that he can dispose of the bacteria as well as a normal dog. Since the injury to the antibacterial defence requires at least this amount of time for repair, it follows that when the animal has made a good recovery from shock immediately, but dies within 48 hours, the cause of death may be due to infection with relapse into septic shock.

(2) In a search for a defect among the several components of the antibacterial defence the effect

* Muscle from normal dogs was not lethal.

of plasma from a shocked dog was compared with that of the normal dog upon the phagocytic index of normal granulocytes. This phagocytic index was found to fall progressively the longer the duration of shock (Schweinburg et al., 1955).

Additional data on the effect of shock on the antibacterial defence were derived from an exploration of the following considerations:

(1) We do not know whether the tissue disintegration products of bacterial activity are a factor in the collapse of the peripheral circulation. Whether they are or not, we do know that bacterial endotoxins are capable of inducing fatal shock (Weil et al., 1956; Delaunay et al., 1947a). Therefore, if there is a decline in the ability of the shocked animal as compared to the normal animal to inactivate bacterial endotoxins from bacteria to which both are equally exposed, i.e. invaders from the gut and respiratory tract, the unneutralized toxins, which cannot be excreted, may induce irreversible damage to the peripheral vessels, just as they do when a normal animal is subjected to a lethal dose of endotoxin.

To study this question it was necessary to quantitate the sensitivity of the normal and shocked animal to bacterial endotoxins. Since the dog is an unsuitable species in which to do this, the rabbit was used. Rabbits recovering from 2 hours of haemorrhagic shock were found to be at least 100,000 times more vulnerable than normal rabbits to a standardized dose of an E. Coli endotoxin (Schweinburg et al., 1955). Hence shock must produce damage to the systems concerned with detoxification of endotoxins.

(2) Hypothermia applied to the dog in advance of inducing haemorrhagic shock delays the development of irreversibility to transfusion (Friedman et al., 1956). Moreover, the response to transfusion after 6, 7 or 8 hours is uniformly good and sustained, so that recovery seems to be on the way in most instances. But death always occurs 24 to 36 hours later. Since so late a death occurs in only 15 per cent of normothermic animals, a complicating factor rather than the shock itself appears to be the cause of death. This factor was shown to be bacterial activity by the further observation that an antibiotic given at the time of transfusion resulted in recovery of all animals. Hypothermia, therefore, protects the enzyme systems serving the antibacterial defence. This protection is substantial because the mortality in consequence of the antibiotic, which is useless in the normothermic animal when given at the time of transfusion, is zero instead of 100 per cent. Because the protection from hypothermia alone is not complete, and full recovery from the injury requires at least 48 hours, the death which follows in the meantime if no antibiotic is given is clearly due to bacterial activity.

The Properdin-Mg-complement complex of Pillemer is profoundly affected by haemorrhagic shock. Dogs with a normal properdin titre show a rapid decline in this titre to, or nearly to, zero within 2 to 4 hours after the onset of shock. If they are reversible to transfusion, the titre remains low for 4 to 5 days and then rapidly returns to or above normal. Hypothermia prevents this fall during shock, but after transfusion and return to normothermia, the titre falls to zero (Frank et al., to be published).

(3) The vigour of the antibacterial defence depends not only on plasma constituents, but on the ability of the phagocyte to move to the site of challenge, then to engulf bacteria, and finally to lyse them after ingestion. All of these functions are damaged in shock. In the normal rabbit the injection of beef infusion broth into the peritoneal cavity produces an average of 100 million granulocytes within 6 hours. In a comparable experiment on the rabbit put into shock for 2 hours immediately after the injection, there is no mobilization of granulocytes into the peritoneal cavity 4 hours after the transfusion (Rutenburg and Fine, 1956a). The failure of granulocytes to enter the peritoneal cavity is not due solely to defective haemodynamics, because normal haemodynamics are restored by the transfusion. A possible causative factor is the granulocytopenia, which develops shortly after the induction of shock in rabbits (Schweinburg et al., in press).

(4) It is quite clear, as Miles and Niven (1950) and Mahoney et al. (1945) have shown before, that the inflammatory response to infection is considerably weakened by the state of shock. This is not only because fewer phagocytes reach the site of challenge, but also because there is a circulating toxin which impairs the phagocyte morphologically and functionally (Rutenburg and Fine, 1956b). Thus, normal granulocytes in normal plasma at 37°C retain their normal morphology

for a number of hours; but when immersed in plasma from shocked rabbits, they show gross distortion, with loss of granules, disruption of the cytoplasm, and an eccentric, crescent-shaped, blurred nucleus. Normal granulocytes immersed in shock plasma are, as stated above, not only less efficient in phagocytosing bacteria, but their ability to lyse the ingested bacteria is considerably weakened. Whether the leucotoxin in shock plasma so demonstrated is a bacterial endotoxin is not yet known.

Having in mind these data, we can return to the observation that antibiotics given in advance are effective,* whereas when given during shock they are not. This difference in the effect of timing is true also for other drugs. Thus, dibenzyline given prior to shock enables the rat and the dog to endure an exposure to haemorrhagic shock to which the untreated animal succumbs (Remington et al., 1948). But it is ineffective if given after shock has been induced (Jacob, 1956). Since dibenzyline exerts a haemodynamic effect one might expect it to act differently in the shock state than in the normal state. On the other hand, antibiotics can be expected to act the same way whether given before or after shock is induced, except in so far as defective flow during shock delays the achievement of an effective tissue concentration. This delay seems insufficient to account for the critical difference in the effect of timing. Is it possible that a vital component in the antibacterial defence begins to fail immediately after shock develops, and that there is a simultaneous elaboration of bacterial endotoxins sufficient eventually to inflict irreversible damage, even if a subsequent complete halt in bacterial activity is achieved by a delayed antibiotic? If so, what is the evidence for the presence of bacterial endotoxins in the blood or tissues?

A toxin responsible for the development of irreversibility to transfusion was shown to be present in the blood of dogs and rabbits in haemorrhagic shock by a technique like that described above for the study of the toxic properties of mashed liver from normal and shocked dogs (Schweinburg et al., 1958). Normal dogs bled a litre of blood and given in exchange a litre of blood from a dog dying in advanced haemorrhagic shock are not adversely affected. On the other hand, dogs in shock for only 2 hours, and transfused with such shocked donor blood instead of their own, fail to recover. At death, which occurs within a few hours or before 24 hours, they show intramural haemorrhage of the intestine, necrosis of the intestinal mucosa, and a variable amount of blood in the lumen of the gut—a process analogous to what one observes in dogs given a lethal dose of endotoxin (Lillehei, 1958). The toxicity of such donor blood is indicated by the observation that as little as 100 ml added to an average transfusion of some 800 ml is lethal for the recipient. Similar results are obtained with Seitz-filtered blood from dogs in shock from peritonitis. Donor blood from dogs in tourniquet shock is also toxic, and produces more severe bleeding from the gut and more necrosis of the intestinal mucosa than blood from dogs in haemorrhagic shock. In general the results in rabbits are like those in dogs.

What is the toxin? Because it acts to produce an intestinal injury similar to that inflicted by a bacterial endotoxin, one suspects that it is a bacterial endotoxin. The latter is a lipopolysaccharide, and, when injected into the circulation, will be found entirely confined to the lipopolysaccharide fraction of the plasma. We found that the toxicity of plasma from shocked animals is present exclu-

* We should here refer to the failure of another group of investigators (Hardy et al., 1954) to confirm our results with the prophylactic use of aureomycin, which they found conferred some protection, but far less than we obtained. The reasons are not clear, but certain points should be made here: (1) Their dogs have a low to absent properdin titre, while 60 to 70 per cent of ours have a normal properdin titre. (2) Half of their dogs were found to have a bacteraemia, whereas the blood of our dogs was regularly free of bacteria. The discrepancy in results might be explained on the basis of the flora in their laboratory being resistant to aureomycin. Indeed, when we repeated our own observations with aureomycin three years after our data were first gathered, we too found aureomycin ineffective. Gyorgy (1954) had a similar experience. After four years of use of this drug for the prevention of liver necrosis in rats on a mecrogenic diet, the drug became totally ineffective. But on repeating the study in two other laboratories where no antibiotics had been used, he confirmed his original findings. Mindful of this we then gave antibodies to a few dogs in the kennels before reaching the laboratory, and obtained protection when the shock experiment was performed immediately on arrival in the laboratory. In rabbits, we and others (Baez, 1955) have consistently obtained protection against irreversibility in a haemorrhagic shock with polymyxin, bacitracin and neomycin without encountering resistance to them.

sively in this fraction, whereas no component of the plasma of normal animals is toxic (Ravin et al., 1958). Concentrated extracts of the lipopolysaccharide fraction, as well as the whole fraction, from rabbits and dogs display all the known properties of endotoxins. They are pyrogenic when given intravenously; they induce resistance to endotoxins, and on repeated administration they, like endotoxins, induce resistance to an otherwise lethal exposure to haemorrhagic shock (Smiddy and Fine, 1957). Electrophoretic and chromatographic data on these materials is still preliminary, but as far as they go they are consistent with those on known endotoxins.

What is the source of this toxin? Because it is eliminated by the prophylactic administration of entirely nonabsorbable antibiotics (polymyxin and bacitracin) given orally, as well as by the same antibiotics given parenterally (Schweinburg et al., 1957), it is a product of the intestinal flora. It may be derived from intestinal bacteria after invasion, or it may be endotoxin continuously entering the circulation from the gut by passive diffusion. Direct evidence that the latter process takes place is being sought currently from experiments measuring the amount of labelled lipopolysaccharide in the blood several hours after placing viable E. Coli labelled with P.32 in the gut. Final proof awaits such data as (1) the P.32/hexose ratio of the labelled polysaccharide in the plasma compared to the corresponding ratio in the endotoxin of the labelled bacteria; and (2) chemical identification of the hexoses in one product with those of the other.

Identification of the toxin as endotoxin is strongly suggested by the capacity of the toxic plasma from shocked rabbits, as stated, to induce tolerance to endotoxin (this evidence, still unpublished, is only preliminary), and to induce tolerance to an otherwise fatal exposure to haemorrhagic shock (Smiddy and Fine, 1957). The behaviour of such resistant animals is reminiscent of the tolerance of dibenaminized animals to haemorrhagic shock (Smiddy et al., 1958). These two methods of inducing protection appear to involve apparently unrelated mechanisms. But the work of Delaunay and his colleagues (1947b) and later of Thomas (1956), has demonstrated that bacterial endotoxin produces peripheral vascular damage by intensifying adrenergic activity. Recently we have also observed protection by reserpine, which, according to Burn and Rand (1958), eliminates noradrenaline from the peripheral nerves.

Why does endotoxaemia develop in the animal in haemorrhagic shock?* We have stated that the normal antibacterial defences are weak in shock; but it may be helpful for eventually more effective prophylaxis and therapy to try to define more precisely the nature of the deficiency. Because our hypothesis relates primarily to endotoxins, we have been especially concerned to investigate the reticulo-endothelial system (R.E.S.), which is the main endotoxin-detoxifying system (Carey et al., 1958; Thomas, 1956), to see how alteration of its potential affects the host's response to haemorrhagic shock. Injury to the R.E.S. was inflicted by giving a "safe" dose of Thorotrast (3 ml/kg intravenously of 25 per cent suspension of Thorium dioxide), which is rapidly ingested by the R.E.S. (Cremer and Watson, 1957). The recipient rabbit shows no overt disturbances and survives without noticeable harm. Such a rabbit, however, dies if some 3 hours later it is given an otherwise nonlethal dose of endotoxin, or is exposed to haemorrhagic shock of only 5 minutes duration, or if it is given a small additional dose of Thorotrast. It also dies if it is given a nonabsorbable antibiotic orally! In all of these circumstances there is a severe Shwartzman reaction and intramural haemorrhage in the gut at death! Elsewhere we discuss the evidence affirming that the Shwartzman reaction and the death in these animals is due to an endotoxaemia (Ravin et al., 1958). Thus we are led to reaffirm the view that endotoxins are constantly available, and will produce peripheral vascular collapse if the R.E.S. is damaged. Haemorrhage, injury from tourniquets, or infection sufficient to produce shock are merely different ways of inflicting severe damage on the R.E.S.

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BOOK REVIEW

Modern Trends in Anaesthesia. Edited by Frankis T. Evans, M.B., B.S., F.F.A.R.C.S., D.A., and T. Cecil Gray, M.D., F.F.A.R.C.S. Published by Butterworth & Co. Ltd., London. Pp. 318; illustrated. Price 67*s.* 6*d.*

This latest addition to the *Modern Trends* series will be a distinct asset to practising anaesthetists and all doctors interested in the specialty or any of its many ramifications with other branches of medicine. It represents a welcome attempt in book form to give both an up-to-date and an inquisitive view of the many aspects of present-day anaesthesia, and presents—so far as they are known—the physiological and biochemical implications of the subject rather than the details of practical technique.

If, for the purpose of discussion, it is accepted that most people can give an anaesthetic after a reasonable period of training and practice, then this volume might well in part be rated as an exposition of what happens during and after anaesthesia, and therefore as an expert review of information on when and, perhaps more important, when not to do certain things. The result is that progress in the specialty can be seen as an attempt—albeit an incomplete one at present—to maintain the patient in a state wherein reaction to operation, anaesthetic and disease are absent.

A great part of the work deals with our present knowledge of the pharmacological agents used in anaesthesia, and the trends toward better drugs, but their modes of action and clinical use are discussed. The growing needs of both physician and surgeon and their relationship to the anaesthetist are well illustrated by chapters on newer conceptions of consciousness, respiratory physiology, hypothermia, cardiorespiratory pumps, surgical trauma, anaesthesia and disease, the anaesthetist and the paediatric unit, and the pituitary-adrenal system.

To blend both basic science and clinical medicine happily and in a manner calculated to satisfy the laboratory worker and the clinician is no easy task, yet, for the most part, this has been achieved. There are one or two chapters that do not quite match up to the general high standard of the book, but the editors can consider that they have chosen their team of contributors well. They have been wise to include recognized authorities in fields other than the purely anaesthetic, thus illustrating both the broadness of the subject and the scope in it for further study.

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THE EVOLUTION OF ANAESTHESIA

BY

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(*Continued from Vol. 30, page 147*)

ETHER

The discovery of di-ethyl ether has been attributed to Jābir ibn Hayyān, an Arabian philosopher who flourished in the eighth century and was a close friend of Ja'far al-Barmāki, the Wazīr to Harun ar-Rashīd, immortalized in the "Thousand and One Nights". Similarly, Raymund Lull or Lully, a Majorcan alchemist of the thirteenth century, has also been credited with the discovery, but there seems to be no evidence to substantiate these claims. The curious reader is referred to an article, "The Discovery of Ether", *Anaesthesia* (1949), **4**, 188, for a fuller consideration of these persons.

The first unequivocal description of ether, under the name, "oleum vitrioli dulce" ("sweet oil of vitriol"), occurs in Conrad Gesner's edition of the works of Valerius Cordus, published in Strasburg in 1561 (*De artificiosis extractionibus*, Lib. 3, Cap. 12). A second, and more accurate, edition was prepared by Peter Condemberg ten years later. "Oil of vitriol" was the name of what we now call sulphuric acid; the "sweet oil" was obtained by the distillation of sulphuric acid and spirits of wine. Cordus advocated the internal use of ether in a dose of one to three drops in a moderate quantity of wine as a remedy for such diverse disorders as ulcer of the bladder and pneumonia.

In 1605, there appeared the first edition of Paracelsus' *Opera Medico-chemica sive paradoxa*. It contains an account of the action of ether on domestic fowls. "Of all the extracts of vitriol, this particular one is the most important, being stable. Furthermore, it has an agreeable taste, so that even chickens take it gladly, and thereafter fall asleep for a long time, awakening unharmed. In view of the effect of this vitriol, I think it especially noteworthy that its use may be recommended for painful illnesses, and that it will mitigate the disagreeable complications of these."

Paracelsus had died in 1541, and Cordus three years later, the works of both appearing posthumously. It is generally believed that ether was discovered about 1540, at which time Cordus and Paracelsus seem to have been together. It is, therefore, impossible to apportion the credit for the discovery between them.

Ether was occasionally synthesized during the next two centuries; thus, the Hon. Robert Boyle describes the process in his *Experiments and notes about the producibleness of chymicall principles* (1680); and Sir Isaac Newton also mentions it in his *Optics* (1704). It was not, however, until the German chemist, Froben (Frobenius) wrote *An account of a spiritus vini aetherus* in the Philosophical Transactions of the Royal Society in 1730, that the "sweet oil of vitriol" became well known or acquired its present name. The place of ether in medical treatment became established in 1743, probably because in that year there was published *An account of the extraordinary medicinal fluid, called aether*, by M(atthew) Turner, Surgeon, in Liverpool, who recommended the administration of two teaspoonfuls of ether in wine for various complaints, and also for headache, of which he writes, "In stubborn cases, it will likewise be serviceable to snuff a little of the ether up the nostrils, either alone or mixed with equal parts of lavender water, Hungary water or Brandy, or it may be convenient to apply a bit of linen rag, wetted with aether, up the nostrils." In 1795, Richard Pearson published his *Short account of the nature and properties of different kinds of airs*, in which he stated that he had found that the inhalation of the vapour of ether by patients with phthisis was very beneficial; "It abates the hectic heat, relieves and often removes the dyspnoea, and promotes and often

improves the expectoration." By 1805, Dr. John Warren of Boston, Massachusetts, father of Dr. John Collins Warren, had adopted Pearson's treatment for phthisis; and Nysten's *Dictionary of Medical Sciences* (1815) speaks of the inhalation of ether as familiarly known for mitigating the pains of colic.

The stupefying effect of nitrous oxide had been described in 1800 by Humphry Davy. In 1818, the *Journal of Science and the Arts*, published by the Royal Institution, contained the following anonymous statement, "When the vapour of ether mixed with common air is inhaled, it produces effects very similar to those occasioned by nitrous oxide. . . . It is necessary to use caution in making experiments of this kind. By the imprudent inspiration of ether, a gentleman was thrown into a very lethargic state, which continued with occasional periods of intermission for more than thirty hours, and a great depression of spirits; for many days the pulse was so much lowered that considerable fears were entertained for his life". A method of vaporization of ether by means of a bottle, into the upper part of which a tube could be introduced for a variable distance, was also described. In 1819, there appeared, in the *Annals of Philosophy*, a *Memoire on sulphuric ether*, by John Dalton, and this is the classical description of the chemical and physical properties of ether.

Christison, in the second edition of his work, *On Poisons* (1836) related the case of a young man who had been rendered completely insensible by the vapour of ether, but such occasional accidents did not deter people from indulging in the inhalation of ether, which was by now well known, especially in the United States of America, as an intoxicant, and so-called "ether frolics" became popular in that country. From 1839 to 1841, William E. Clarke of Rochester, New York, then a student, and later a physician in Chicago, held a number of such parties, and it has been said, on what authority is unknown, that W. T. G. Morton was one of his guests on these occasions. Emboldened by his experience, Clarke, in January 1842, at Rochester, administered ether on a towel to a Miss Hobbie, and one of her teeth was then painlessly extracted by a dentist named Elijah Pope. Neither Clarke nor Pope published an account of the transaction, which seems to have been the first occasion on which anaesthesia with ether was undertaken, for we may discount the note in the *Edinburgh Medical and Surgical Journal* of April 1847, which refers to a case of ether anaesthesia "thirty years" before.

During an "ether frolic" at Anderson, South Carolina, in 1839, a youth named Wilhite forced a negro boy to inhale ether until he became insensible. Wilhite is believed to have given an account of this experience to Dr. Crawford Williamson Long of Jefferson, Georgia, already accustomed to such diversions, who, in March 1842, persuaded a patient, from whose neck he was about to remove a tumour, to inhale ether until insensible. The operation was performed without pain and recovery was uneventful. The event was recorded by Long in his ledger: "James Venable, 1842. Ether and excising tumour, $2.00." Two similar operations were subsequently performed on Venable, and Long also used ether on three other patients in the following two years, after which he gave up its use, nor did he publish any account of his discovery until after the first public administration of ether by Morton.

According to the report of a select committee of the American House of Representatives in 1852, "Late in the autumn of 1844, Dr. E. E. Marcy of Hartford, Connecticut, as appears from his own affidavit and that of F. C. Goodrich of Hartford, suggested to Dr. Wells to substitute sulphuric ether for nitrous oxide, and informed him of its known effects and how to make it. Marcy 'administered the vapour of rectified sulphuric ether in my (his) office to a young man . . . and, after he had been rendered insensible to pain, cut from his hand an encysted tumour of about the size of an English walnut'." A slight doubt is cast upon this statement by the fact that it was not until December 10, 1844, that Horace Wells became interested in nitrous oxide; however, the story is probably otherwise true. A Dr. E. R. Smilie of Boston also asserted to the same committee "that he had employed successfully an etherial (sic) tincture of opium to subdue pain under the knife. He states that he applied this tincture by inhalation in the Spring of 1844; that he opened a serious abscess on the neck of the late Mr. John Johnson, while he was rendered unconscious of pain from the operation by this tincture". This story has little appearance of truth.

The committee further stated that in March, 1846, there appeared, in the *Paris Medical Gazette*, "an account of remarkable experiments performed by M. Ducos, by ether, on animals, exhibiting most of the phenomena since witnessed in the human body".

In July 1847, when the "ether controversy" between Morton and Jackson was developing, Morton presented, through M. Arago, a *memoire* to the Academy of Arts and Sciences at Paris. This account is probably substantially correct. He stated that, in the summer of 1844, he being then in dental practice and also studying medicine under Dr. Charles T. Jackson of Boston, he discussed with the latter the problem of destroying the nerve of a tooth. Jackson told him that, some years before, he had successfully extracted a tooth after applying ether topically, and provided Morton with a bottle of the liquid. Morton used it by direct application. Jackson, on one occasion, saw Morton use it unsuccessfully in this way, but made no suggestion that he should get the patient to inhale the vapour. Later, however, Jackson did tell him what was then known concerning the inhalation of ether, and Morton, reading the subject up, came to the conclusion that there was nothing dangerous in the method. He became ill, and, while in the country convalescing, experimented unsuccessfully with some ether, locally obtained, on animals and birds.

In the winter of 1844–45, Morton assisted Horace Wells in the unsuccessful demonstration of nitrous oxide at the Massachusetts General Hospital. Morton's interest in ether was reawakened in the Spring of 1846 when one of his dental students, Thomas R. Spear, told him of his experiences at "ether frolics". Morton then administered ether to his dog, a water spaniel, "inserting his head in a jar having sulphuric ether at the bottom. This was done in the presence of two persons at my house at West Needham, where I reside during the summer months. After breathing the vapor for some time, the dog completely wilted in my hands. I then removed the jar. In about three minutes he aroused, yelled loudly, and sprung some ten feet into a pond of water". In August, Morton inhaled ether himself from a handkerchief, and also gave it, without success, to his two students, Spear and Leavitt.

Late in September 1846, Morton had the idea that the results might be more successful if he administered the vapour from a gas bag. Accordingly, he went to borrow a bag from Jackson whom he asked if it were possible to give ether vapour in order to relieve pain. Jackson said that it was, spoke of "ether frolics", advised him to use Burnett's ether, since this was the purest, and also gave him a flask and glass tube, considering this better than a gas bag. Morton now tried again the effect of ether on himself, with complete success.

On September 30, in the evening, a man called Eben Frost "came in, suffering great pain and wishing to have a tooth extracted. He was afraid of the operation, and asked if he could be mesmerized. I told him I had something better, and, saturating my handkerchief, gave it to him to inhale. He became unconscious almost immediately. It was dark, and Dr. Hayden (a dentist) held the lamp, while I extracted a firmly rooted bicuspid tooth. There was not much alteration in the pulse, and no relaxation of the muscles. He recovered in a minute, and knew nothing of what had been done to him".

Morton next called on Jackson, told him what he had done, and asked for a certificate to the effect that it was harmless; this Jackson refused to give. Morton also obtained permission to demonstrate his discovery at the Massachusetts General Hospital; meanwhile, he used ether several times in his surgery, but not very successfully. One child, who vomited, was pronounced by a physician to have been poisoned, and the patient's friends threatened legal proceedings.

On the morning of October 16, 1846, Morton obtained a glass inhaler from an instrument maker called Chamberlain, and used this on the patient, Gilbert Abbott, with that success which has since become so famous, and which proved the efficacy of ether as a reliever of pain during surgical operations. Morton subsequently administered ether at the hospital and elsewhere on frequent occasions.

On October 23, 1846, Jackson called on Morton and, having heard that a patent was being taken out, asked for payment for his share in the discovery. Eventually, Morton allocated a 10 per cent share in the patent to Jackson, which would seem to have been a generous award. Morton's account is corroborated at a number of points by

the evidence of his patients and colleagues and is probably reasonably accurate.

The subsequent efforts of Jackson to obtain the full credit for the discovery need not detain us here: it is sufficient to record that his pertinacity in this direction led to the defeat of Morton's claims in the United States Senate so that the discoverer, whose patent had been tacitly ignored by the government, never received any financial reward.

News of Morton's successful demonstration soon spread across the Atlantic; H. J. Bigelow's letter, written on November 28, 1846, reached Boott in London in three weeks. The latter immediately sent a communication to the *Lancet* and wrote to Robert Liston, then Professor of Clinical Surgery in the University of London. On December 19, under Boott's direction, his niece, Miss Lonsdale, had a tooth extracted by a Mr. Robinson. Ether was administered by means of an apparatus made by Hooper. Boott wrote again to the *Lancet*, describing the procedure, "the whole process of inhalation, extracting and waking was over in three minutes", he said.

On December 21, 1847, Liston, at University College Hospital, performed two operations under ether anaesthesia, an amputation through the thigh, and an avulsion of the toe-nail. The apparatus employed, which was similar to Hooper's, was designed by an instrument maker called Squire, who probably administered the anaesthetics, and who subsequently developed a practice as an "etherizer". The success was such that the future of anaesthesia was assured.

Naturally, it was in London that the new idea flourished most in Europe, but the news spread: in December it had reached France; on the 24th de Lamballe had a successful anaesthetic at the Hôpital St Louis, and on January 12 J. F. Malgaigne described five anaesthetics, given by himself, before the Académie de Médecine in Paris. He used to administer ether through a tube inserted into the nostril, and this technique won a certain popularity in France, but was soon displaced by Charrière's apparatus, which was an improved version of Hooper's and Squire's inhalers.

The successful use of ether anaesthesia for surgical operations stimulated James Y. Simpson, Professor of Midwifery in the University of Edinburgh, to employ this agent in obstetrics, and his first operation with this anaesthetic was successfully (so far as the mother was concerned) undertaken on January 19, 1847, and subsequently reported in the *Edinburgh Monthly Journal of Medical Science*. This use of anaesthetics, however, raised a storm of protest which was only slowly quelled, and it was some years before anaesthesia in midwifery became general. Since, by then, ether had been largely displaced by chloroform, introduced by Simpson in November 1847, the account of the midwifery dispute properly appertains to the consideration of that agent. In France, anaesthesia for midwifery was reported by Dubois on February 13, 1847; the first obstetrical anaesthetic in the United States of America was undertaken by Dr. N. C. Keep of Boston on April 7, 1847, and the second, an instrumental intervention, on May 5, Walter Channing being the surgeon.

Meanwhile anaesthesia was spreading throughout the world. Ether was popularized in Germany by Dieffenbach, then in his last year of life, whose inhaler was very similar to the glass globe used by Morton. The first scientific account of anaesthesia in Germany was published by von Siebold in the *Proceedings of the Royal Society of Sciences* (Goettingen) on May 8, 1847, but Heyfelder of Erlangen had begun the extensive use of ether anaesthesia as early as January 17, while Schuh of Vienna used anaesthesia on January 27, and Behrend of Berlin and Halla of Prague on February 6. The first anaesthetic in Sweden seems to have been given by E. G. Palmgren on February 9, and in Spain by de Argumosa y Obregon on February 14. By July 1847, Parker had used ether in China and, before this, the subject had been taken up on the South American continent.

At the same time, other methods of administering ether were sought. During 1847, no less than four people (Pirogoff, Roux, y'Yhedo and Duprey) experimented with the rectal administration of liquid ether, with or without the addition of water: Pirogoff reported eighty-one cases with two deaths.

However, the most important anaesthetic event of the year 1847 was undoubtedly the publication of John Snow's *On the Inhalation of the Vapour of Ether*. Snow's attraction to the subject of anaesthesia, brought about by Squire, was acci-

dental, but his fertile brain was ready to respond to the stimulus, and the assiduity and eagerness with which he turned to the investigation of the new science are revealed in his writings: it is not too much to say that he was the first to understand and give clinical appreciation to the physical properties of ether vapour and its pharmacological effects. Among other things, his book contains a description of the stages of ether anaesthesia, an accepted classification which was to remain the basis of clinical anaesthesia with ether until it was modified by Guedel in 1920. Perhaps more important was Snow's influence on the design of apparatus; he was later (1858) to write:

> "When the inhalation of ether was first commenced, the inhalers employed consisted generally of glass vases containing sponge, to afford a surface for the evaporation of the ether. Both glass and sponge being very indifferent conductors of caloric, the interior of the inhalers became much reduced in temperature, the evaporation of ether was very much checked, and the patient breathed air much colder than the freezing point of water, and containing very little of the vapour of ether. On this account, and through other defects in the inhalers, the patient was often very long in becoming insensible, and, in not a few cases, he did not become affected beyond a degree of excitement and inebriety."

In addition to facilitating the evaporation of the ether by maintaining it at a nearly constant temperature, Snow's inhaler was designed with tubes of a sufficient diameter to minimize the resistance to airflow.

The introduction of chloroform towards the end of 1847 led to the virtual abandonment of ether in many parts of the world. The North American continent, however, generally remained faithful to ether, and it was there that, in 1853, Squibb revolutionized the commercial manufacture of this highly inflammable substance. In 1866, B. W. Richardson invented his ether spray, at first intended to be used with a volatile hydrocarbon called rhigolene, for the production of local anaesthesia by freezing.

The defection from ether lasted in England until at least 1872, and, on the Continent, until almost the end of the century. The first advocate of a return to this peculiarly safe drug was J. W. Haward of St. George's Hospital, who read a paper on the subject before the Royal Medical and Chirurgical Society in October 1871; but the reintroduction of ether was really due to two men, to B. J. Jeffries of Boston, Mass., and Joseph Clover. Jeffries visited England in 1872 and demonstrated the method at that time in use in America, "a towel rolled into a cone, with a napkin or sponge pushed to the top of the inside . . . to pour our ether on". His enthusiasm awakened a response among those who had already become seriously alarmed by the never-ceasing toll of death taken by chloroform, and, in spite of the technical difficulty of administering ether compared with chloroform, a considerable number of surgeons adopted this method. Clover set the seal on this decision by the introduction, in 1872, of his method of procuring the insensibility of the patient by means of nitrous oxide, and continuing the anaesthetic with ether, thus avoiding the unpleasant sensations which were inevitable with a slow ether induction. Clover's "Combined Gas-and-Ether Apparatus", which was received with a measure of enthusiasm, appeared in 1876, after much industrious experiment, and this was followed the next year by his "Portable Regulating Ether Inhaler", which, both in its original form and as modified by Hewitt (1901), was still in use sixty years later.

Parallel with the introduction of the nitrous oxide-ether sequence, the use of "open drop" ether was developed, particularly by Lawson Tait, who favoured "anhydrous methylated ether". This method was also used by Allis, who published an account of his mask in the *Philadelphia Medical Times* of 1874. It was not until 1907 that Bellamy Gardner introduced the frame-mask still used for this purpose. In 1876, Lawson Tait devised his warmed ether inhaler, the intention of which was to reduce the incidence of pulmonary complications. By means of a piston, liquid ether was pumped, one drachm at a time, into a glass vaporizing chamber immersed in water which was heated by a spirit lamp. The ether vapour was conducted to the patient by means of a rubber tube, four or five feet long, which Tait believed to be long enough to avoid the danger of an explosion from the ignition of the ether vapour by the flame of the spirit lamp. A somewhat similar apparatus was introduced by R. W. Carter in 1896. In this, the reservoir of a Junker's inhaler was warmed by burning "Japanese Tinder".

The revival of ether on the Continent began in 1877 with the work of Gustave Julliard of Geneva, who adopted a semi-open technique, but it was

not until the late 1890's that the use of ether became general. In 1884, Mollière of Lyons resuscitated the rectal administration of ether, using, however, the technique of insufflation of the vapour instead of instillation of the liquid, as in the earlier methods.

By the beginning of the twentieth century, ether was firmly re-established and the famous nurse-anaesthetist, Alice Magaw, was able to report 14,000 cases in 1906, but the end was in sight. In 1910 W. D. Gatch developed an apparatus for the administration of nitrous oxide and ether simultaneously, also permitting the use of fractional rebreathing, of which he was a confirmed advocate. Teter, Gwathmey and others developed similar machines, and the use of a stream of nitrous oxide and oxygen to vaporize ether came into fairly general use at the time of World War I. The first Boyle machine, the outcome of a visit by H. E. G. Boyle to the United States of America, appeared in 1917, and his apparatus, with modification, is now that which is most commonly used in this country.

The cost of the new machines was considerable and, in Britain at least, the general standard of anaesthesia did not develop rapidly in the inter-war period. Ether, administered by open drop or by means of the Clover Inhaler, continued to be used alongside the "nitrous oxide with minimal ether" technique, a method in which the word "minimal" was interpreted very broadly. In 1920 Arthur E. Guedel issued the revised description of the stages of anaesthesia, including the subdivision of the third stage into four planes, and emphasizing the respiratory changes occurring with increasing depth of ether anaesthesia.

The rectal route once again became popular with the introduction of the "colonic oil-ether" method of Gwathmey in 1913, and this continued to be used, in obstetrics at least, until about ten years ago.

Some other drugs, rather similar to di-ethyl ether, have been introduced from time to time. B. W. Richardson, for example, experimented with a great many, as did Lawson Tait. One interesting development was the "construction" of di-vinyl ether, suggested by Leake and Chen in 1930. The successful use of ethylene, a rather weak anaesthetic, gave rise to the idea that an ether composed by the conjunction of two molecules of ethylene would prove a satisfactory compound. The drug was, at last, manufactured after considerable difficulty, and, while it achieved some measure of success and is still employed, especially for children, its influence on the discovery of new plastics was probably of much greater importance than the part which it has played in anaesthesia. Krantz and his co-workers have also sponsored the introduction of various ethers in the last twenty years, chief of which is N-methyl propyl ether, but none has proved popular.

Since World War II, the introduction of the relaxants and the extended use of the surgical diathermy apparatus have militated strongly against the use of ether, and it is now unusual for this substance to be used as the sole, or even as the main, agent of anaesthesia. Nevertheless, ether is still an important tool in the hands of the anaesthetist, and it will long remain so. More than a hundred years of almost continuous use have led to the building up of a body of experience with ether which is probably greater than that of any other drug used by the medical practitioner. Because of this knowledge, and because of its inherent property of safety, the experienced anaesthetist will often make use of ether in cases in which the patient's physical condition gives rise to alarm, and, should some great emergency necessitate the use of a number of untrained, or only partly trained, anaesthetists to cope with a sudden influx of casualties, ether will again be used, as it was by the inexperienced Morton, and with equal safety and success.

NITROUS OXIDE

Nitrous oxide was discovered by Joseph Priestley, whose pioneering experiments with gases have ensured him an honourable place in the history of science. He was the son of a cloth-dresser, and was born in London in 1733. After attending a Dissenting Academy at Daventry, he became a Unitarian minister, serving at Needham Market, Nantwich, Mill Hill (Leeds), Birmingham and Hackney. In 1794 he emigrated to America, where he died ten years later in his 71st year. Priestley wrote a number of religious works, and also dabbled in political affairs. His reply to Burke's *Reflections on the French Revolution* led to the burning of Priestley's house by the mob (1791).

It was during his stay in Leeds that he became interested in the nature of air, and his discoveries earned him the Fellowship of the Royal Society, of the French Academy of Sciences, and of the St. Petersburg Academy. The assistance of the Earl of Shelburne, who fitted up a laboratory for Priestley at his house at Calne, enabled him to pursue his experiments for some time without interruption.

Throughout his life, Priestley was bedevilled by the Phlogiston Theory of Stahl, and he thus never came to understand the nature of the chemical reactions which he demonstrated. The discovery of nitrous oxide (dephlogisticated nitrous air) is described in Priestley's *Experiments and Observations on Different Kinds of Air* (1775); unfortunately the event is undated, but it ensued upon the discovery of nitric oxide (nitrous air), and is therefore to be related to the second half of 1772 or, at latest, early 1773.

Nitrous oxide remained a chemical curiosity until its further investigation was undertaken by Humphry Davy. This eminent scientist had been born at Penzance in 1778; in 1795 he was apprenticed there to a surgeon called Borlase. In 1798, he became superintendent of the Pneumatic Institute, opened in that year at Clifton, by Dr. William Beddoes, whence he moved to the Royal Institution in 1801. He became a Baronet in 1818 and was elected President of the Royal Society two years later. He died in 1829, at the age of 55. Davy's interest in chemistry seems to have begun at Penzance in 1797, and it was there that his attention was drawn to nitrous oxide on reading an essay by Dr. S. Latham Mitchill of New York, in which nitrous oxide was denounced as the cause of febrile disorders. Davy prepared the gas, inhaled it, and, noticing its intoxicating effect, renamed it "Laughing Gas". This investigation was the direct cause of Davy's appointment to the Pneumatic Institute; while there, he pursued his researches with the gas, and, in 1800, published his findings in the important book, *Researches Chemical and Philosophical chiefly concerning Nitrous Oxide . . . and its respiration*, wherein he described the analgesic effect of nitrous oxide and suggested that it might be used during surgical operations "in which no great effusion of blood takes place".

Davy's advice fell on deaf ears, but the laypublic exhibited an increasing interest in "Laughing Gas", an interest which was catered for, especially in the United States of America, by itinerant chemists. The medical profession held aloof from the gas, and there is no evidence that it was used by Hickman or anyone else until 1844. The actual use of nitrous oxide as an anaesthetic occurred in the following way. An itinerant chemist, Gardner Quincy Colton, visited the town of Hartford, Connecticut, and, on December 10, 1844, demonstrated the intoxicating effects of "Laughing Gas". In the course of the demonstration, members of the audience were allowed to inhale the gas, and one of these, while still under the influence of it, knocked his shin against a bench with sufficient violence to draw blood. This incident was observed by a dentist, Horace Wells, who was also in the audience, and who noticed that, although the injury must have been extremely painful, the victim appeared to be completely oblivious to it; indeed, when Wells apprised him of it, he was at first incredulous. Wells immediately realized the significance of the incident and, on the following morning, he permitted Colton to administer nitrous oxide to him while another dentist, John M. Riggs, extracted one of Wells' teeth. Riggs has another claim to fame for, 32 years later, he was to introduce a treatment of pyorrhoea alveolaris which was so successful that the disease came to be known in the United States as "Riggs' Disease".

The experiment of December 11, 1844, was a complete success. Emboldened by it, Wells used nitrous oxide on about a dozen patients, and Riggs also made use of it, the latter on one occasion extracting six teeth at a sitting, without causing any suffering. Wells now communicated his discovery to the chief surgeon at the Massachusetts General Hospital, John Collins Warren (1778–1856), an old student of Astley Cooper and of Dupuytren. Warren's father, John Warren (1753–1815), had preceded his son as professor of surgery at Boston, and, it will be recalled, had advocated the use of the inhalation of ether in the treatment of phthisis. Somewhat reluctantly, John Collins Warren gave permission for Wells to address the students on his discovery and to demonstrate the anaesthetic effects of nitrous oxide on a volounteer. Unfortunately, the demonstration proved a fiasco: anaesthesia was insuffi-

cient, and the volunteer emitted a scream as the tooth was extracted. Wells left the hospital amid the jeers and boos of the students.

The subsequent career of the discoverer of anaesthesia with nitrous oxide was short and tragic. Giving up dental practice, it is said after a fatality, he followed various occupations, became interested in chloroform to such an extent as to become an addict, and finally, in 1848, he took his own life in the Tombs prison at New York, whither he had been lodged following an act of an insane nature: at the behest of a chance acquaintance, he had thrown vitriol at a prostitute. The French Academy of Medicine belatedly acknowledged the importance of his contribution to the discovery of anaesthesia, but news of the award of a gold medal to him did not arrive in America until after his death.

The failure of Wells to demonstrate publicly the anaesthetic action of nitrous oxide led to the abandonment of its use. It had, however, one good result, for it caused W. T. G. Morton, who had been present at the fiasco, to turn his attention to more effective agents, and so to the discovery of the action of ether, the introduction of which obscured for a time the potentialities of the weaker drug.

One man alone seems to have retained his belief in the efficacy of nitrous oxide anaesthesia, and that man was Colton. It is true that both Bigelow and Nunneley gave the gas a trial in 1848: the former thought it inferior to ether, while the latter, who only experimented with it on animals, considered it to be so short acting as to be useless, and was worried by the cyanosis produced. Colton, however, remembered the success which he had had with Horace Wells and, continuing his career as a lecturer, frequently referred to that incident. In 1862, a lady who had attended one of Colton's demonstrations, asked him to administer gas to her for the extraction of teeth. The dentist, Dunham by name, was so impressed that he began to use this agent in his own practice, and, a year later, Colton gave up his lecturing and, in association with Dr. J. H. Smith, opened the Colton Dental Association in New York. Within a very short time, nitrous oxide became the accepted anaesthetic for dental extraction in the United States of America.

News of this development naturally came to Britain, and a few experiments were carried out, notably by Rymer at the National Dental Hospital. The results were encouraging, but little notice was taken, and the introduction of nitrous oxide anaesthesia to Britain was delayed.

One of Rymer's difficulties had been his inability to procure sufficient supplies of the gas. This problem was solved in America by A. W. Sprague of Boston, Mass., who devised an apparatus for the manufacture of nitrous oxide by heating ammonium nitrate, passing it through wash-bottles, and storing it in a small gasometer, from which the gas could be used direct or be drawn off into bladders for use outside the dentist's home. The apparatus was costly, but easy to manage, and gave satisfactory results.

In 1867 Colton demonstrated his apparatus and method at Paris, where he so impressed an American dentist, T. W. Evans, that the latter came to England in the following year, bringing with him Sprague's apparatus: he gave a series of demonstrations at the National Dental Hospital and elsewhere. Evans succeeded in persuading several dentists, notably Alfred Coleman, to make use of the gas, but there was some opposition from B. W. Richardson, who believed nitrous oxide to be unsafe. Following his lead, it was proclaimed that anaesthesia resulted solely from asphyxia when this gas was used, a conclusion which was disproved almost at once by Sanderson and Murray at the Middlesex Hospital, who compared the action of nitrogen with that of nitrous oxide, and showed that, with the latter, consciousness was lost sooner and before cyanosis was pronounced. Later in 1868, the Odontological Society formed a Committee to examine the question, but its reports were disappointing. Meanwhile, Joseph Clover turned his attention to the new agent, and modified his chloroform apparatus (really, Snow's apparatus) for use with nitrous oxide.

The extending use of nitrous oxide in 1868 led to the need for some simpler method for its distribution. The difficulty was overcome by compression into cylinders, not at first under sufficient pressure to cause liquefaction. Cylinders of compressed air had been used as early as 1833 by the Vienna fire-brigade, and in 1856, the Medical Pneumatic Apparatus Co. of London was offering nitrous oxide and other gases in this form, but without attracting much attention. Following the lead of

the Editor of the *British Medical Journal*, Ernest Hart, both Coxeter's and Barth's were providing compressed nitrous oxide in 1869, and, almost at once, the gasometer was abandoned, and the gas was taken direct from the cylinder to the patient. The liquefied gas became available on the American market in 1873.

By the end of 1868, nitrous oxide anaesthesia was firmly established in dental practice throughout Europe and America, and already it had become the custom to prolong anaesthesia by permitting the patient to breathe a limited amount of air. Early in 1869, Professor E. Andrews of Chicago described the use of a mixture of nitrous oxide and oxygen, and similar experiments were also made in England. It was at this time that Alfred Coleman introduced the economical use of nitrous oxide by rebreathing, passing the exhaled gases through slaked lime; this was the first use of carbon dioxide absorption in anaesthesia, although the principle had been understood since the days of the Abbé Fontana.

In 1871, at the time of the reintroduction of ether into English anaesthetic practice, Clover described his nitrous oxide-ether sequence: he developed various types of apparatus for this purpose, all of which were extremely successful, and this method of anaesthesia continued to be much used for some sixty years.

At this time, when the clinical use of nitrous oxide was increasing, and when the anaesthetic action of the gas had already been proved by Sanderson and Murray, French physiologists again put forward the theory that the anaesthesia with this agent was the result of asphyxia, and this remained the orthodox belief until the important work of Paul Bert, who showed that nitrous oxide was a true anaesthetic. In 1878, Bert read a paper to the French Académie des Sciences on the harmlessness of prolonged anaesthesia with nitrous oxide. He said:

"The fact that nitrous oxide must be administered pure indicates that, in order to be absorbed by the organism in sufficient quantity, the tension of the gas must be equal to one atmosphere. In order to achieve this at normal pressure, the gas must be in the proportion of 100 per cent. But let us suppose that the patient is placed in an apparatus where the pressure can be increased to two atmospheres; then one could submit him to the desired tension by making him inhale a mixture of 50 per cent nitrous oxide with 50 per cent air. Thus one could achieve anaesthesia while maintaining the normal quantity of oxygen in the blood; and it follows that the normal conditions of respiration would be preserved. This is what, in fact, has been done; but I must add that, up to the present, I have only experimented upon animals."

Bert's hypothesis was first tested in the following year. The pressure used was 920 mm Hg, an increase of rather more than 20 per cent of the normal; nitrous oxide and oxygen were given in the proportions of 85 and 15 per cent respectively. The result was so satisfactory that a mobile pressure chamber was constructed, but this failed to stand the test of time. Although the anaesthesia was excellent, the cost and complication of the apparatus caused it to be abandoned in the early 1880s. Bert's original hypothesis was, however, borne out by the work of Faulconer, Pender and Bickford in 1949 (*Anesthesiology*, **10**, 601).

About this time, the Russian obstetrician, S. Klikowitch, introduced nitrous oxide and oxygen as an analgesic in labour, a method which has found much favour in Scandinavia, and which led, indirectly, to the invention of a gas-air analgesia apparatus by Minnitt in 1934, self-administration of the gases being advocated by A. E. Guedel in 1912. Minnitt's apparatus had the advantage that it could be used by relatively untrained midwives. In 1883, Bert had turned his attention also to the administration of nitrous oxide and oxygen mixtures at normal pressure, and similar work was done by a Viennese dentist, H. T. Hillischer, who, a few years later, produced an apparatus in which the percentage of nitrous oxide and oxygen could be regulated.

Meanwhile, other methods of prolonging nitrous oxide anaesthesia were being sought. Coxon in 1888 used a stream of gas directed into the patient's mouth during dental extractions; in 1898, Coleman described the nasal mask, a method of administration, however, which both he and Clover had used many years before and which is substantially the same as that employed to-day; in the same year, Hilliard described the use of a naso-pharyngeal tube for the administration of gas during dental procedures.

It was Hillischer's apparatus which stimulated Hewitt to construct a more portable and more easily regulated apparatus. Before 1893, Hewitt had designed an apparatus for administering nitrous oxide, employing a special stop-cock by which the patient could be made to rebreathe or

not, as desired. His nitrous oxide-oxygen apparatus embodied this valve, and was provided with two reservoir bags, one for oxygen and one for nitrous oxide, which were to be kept equally distended by manipulation of the foot-keys controlling the cylinder outlets. The two reservoir bags were separated from the stop-cock by a regulator which permitted a variable proportion of the gases to reach the patient by altering the sizes of the orifices. A modified regulator and stop-cock were described in 1897. Some fifty years later, R. R. Macintosh produced a somewhat similar apparatus, differing from Hewitt's in that, in order to equalize the pressures between the two bags, the oxygen reservoir was placed within the nitrous oxide bag.

Nevertheless, in spite of these developments, in 1901 Hewitt was still advocating the use of a gasometer filled with known quantities of nitrous oxide and oxygen for administering a constant mixture. The focus of development now shifted to the United States where anaesthetic apparatus underwent considerable improvement during the first two decades of the twentieth century. The first machine was designed by S. S. White; it appeared in 1899 and was essentially similar to Hewitt's apparatus. Three years later, C. K. Teter of Cleveland produced another machine along rather similar lines, but incorporating a device for warming the gases, and an ether vaporizer, a device in which he had been preceded by Coleman. In 1906, the Clark apparatus appeared, again incorporating a proportional regulator. This machine may be regarded as the direct ancestor of the first McKesson apparatus, which appeared in 1910, the brain-child of Elmer I. McKesson of Toledo, Ohio. This machine, which has undergone many modifications, was the first of the intermittent flow machines. McKesson introduced fractional rebreathing in the following year; his Nargraf apparatus appeared in 1930, and is still a popular machine in dental practice.

At the same time that McKesson was perfecting his mixing valve (1910), Boothby and Cotton opened the door for the modern continuous flow apparatus by employing a water sight-feed flowmeter. This was somewhat unwieldy, and was improved by J. T. Gwathmey in 1912. Boothby and Cotton also introduced the reducing valve into anaesthetic practice. Other apparatus was designed by Gatch, Heidbrink and Foregger soon afterwards.

American developments aroused the interest of H. E. G. Boyle in this country: his first apparatus was designed in 1917. After a continuous series of modifications, this apparatus is still the most popular machine in the British Isles. The Walton intermittent-flow machine was designed in 1925, while Magill's apparatus appeared three years later. This latter apparatus was fitted with Siebe Gorman dry flowmeters in 1931, and with rotameters in 1937. These latter had been used in industry for some years and their value to anaesthetists was realized first by Magill and, soon after, by Mr. Salt of the Nuffield Department of Anaesthetics at Oxford.

The gas ethylene is somewhat similar as an anaesthetic to nitrous oxide; although rather more potent, it has the disadvantage that it is inflammable. Its anaesthetic properties were first noticed by Luckhardt and Thompson in 1918, and it was introduced into clinical practice five years later, when it immediately became popular in the United States of America. It has not, however, achieved a similar popularity in this country.

This section must close on a more sombre note. After the extensive use of nitrous oxide with remarkable success, especially for dentistry, for three-quarters of a century, the warning of the dangers of anoxia was first sounded by C. B. Courville (*Untoward Effects of Nitrous Oxide Anaesthesia*, California, 1939). Experience has proved the truth of Courville's contentions, and it is now fully realized that nitrous oxide anaesthesia must not be accompanied by reduction in oxygen intake. This has led to the supplementation of nitrous oxide for almost all procedures, a technique which reached its apogee after the introduction of the relaxants. The satisfactory results obtained by this combination led to an extension of its use to the treatment of tetanus, and, once again, a warning has been sounded, this time by H. C. A. Lassen and his associates (*Lancet*, 1956, **1**, 527), who have shown that prolonged anaesthesia with nitrous oxide may cause acute aplasia of the bone-marrow. Nevertheless, nitrous oxide is still one of the most valuable anaesthetic agents we possess, and its future place in anaesthesia would seem to be assured for many years to come.

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